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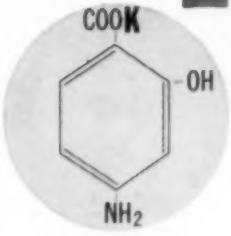

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2. *Cohen, R. V., Malthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations). Read before the American Trudeau Society, Annual Meeting, Milwaukee, Wisconsin, May 23-27, 1955.*

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DETECTION OF EARLY PULMONARY EMPHYSEMA[1,2]

JOHN K. CURTIS, HOWARD K. RASMUSSEN, AND JOHN T. MENDENHALL

(Received for publication May 25, 1955)

INTRODUCTION

A pulmonary function laboratory was established at the Veterans Administration Hospital in Madison, Wisconsin, primarily for the study of patients before and after pulmonary surgery. As many patients undergo lobectomy and pneumonectomy, it appeared important to determine whether or not the overexpanded remaining lung tissue eventually develops emphysema. This is a long-term project and may not properly be concluded until years of follow-up data are available. To be successful in such a study, sensitive methods for detecting early emphysema are necessary. Clinicians have learned that physical examination is unreliable in making the diagnosis of emphysema (1). Roentgenographic studies also are uncertain even in making the attempt to diagnose moderately advanced emphysema (2). Physiologic tests would seem to offer the best possibility of diagnosing emphysema, although there is no single test which is pathognomonic of the condition.

Most investigators of the physiopathology of emphysema have concerned themselves with patients with far advanced involvement in whom varying degrees of dyspnea are already present (3, 4). The single criterion most often used is an elevation of the ratio of residual air to total lung capacity, and it has been stated that the diagnosis of emphysema should not be entertained in its absence. Some investigators have recommended grading the degree of emphysema on the basis of such studies (5). Recently Gilson and Oldham have recommended a battery of tests which they have found useful in detecting this condition in Welsh coal miners (6).

The interest of the present investigators in the significance of reduced maximal breathing capacity (MBC) and elevation of the spirogram to hyperinflation level was aroused by the observation that a number of patients exhibited this phenomenon on their preoperative evaluation. Bronchodilators had no effect except in the occasional patient in whom the emphysema was complicated by asthma. Accordingly, a study was initiated in an attempt to correlate the abnormal find-

[1] From the Veterans Administration, Madison, Wisconsin.

[2] Presented before the Medical Session, as part of *Section 5B*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 25, 1955.

FIG. 1. Patient K. K., 44 years old. Two-second timed vital capacity, 83 per cent; maximal breathing capacity, 98 per cent, with elevated spirogram; single breath of oxygen, 4 per cent. Apico-posterior segment, left upper lobe.

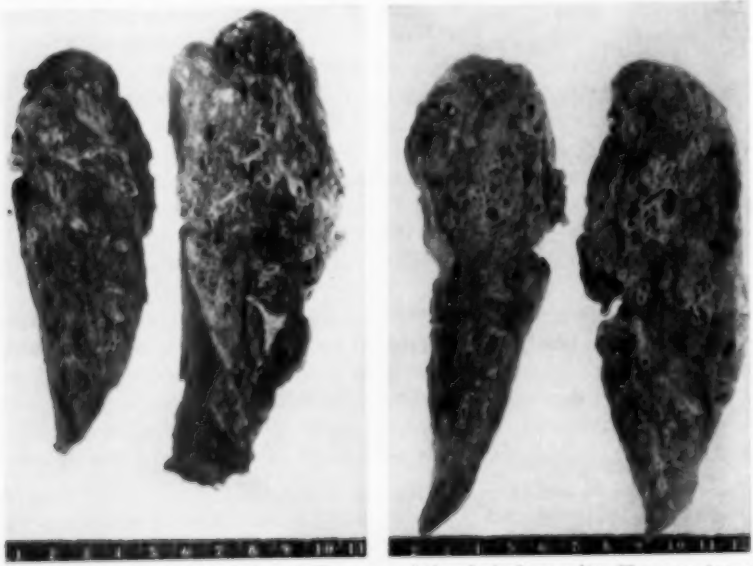

FIG. 2. Patient T. A., 30 years old. Two-second timed vital capacity, 80 per cent; maxi-

ings in pulmonary function with the histopathologic findings in the pulmonary tissue.

MATERIALS AND METHODS

The lungs of all of the patients were carefully inspected by the surgeons at the time of thoracic operation and observations were made by the anesthetists on whether or not emphysema was present. The resected lungs were sectioned and photographed, and microscopic slides were made. Emphysema was considered present when blebs or bullae were found or when destruction of alveolar walls was noted, with multiple widely scattered enlarged alveoli observed grossly. Figure 1 is a photograph of a typical example of early emphysema. Figure 2 is a photograph of sections of lung demonstrating far advanced emphysema. It has not been possible thus far to undertake elastic tissue staining, to study the bronchioles for evidence of obstruction, or to attempt to appraise the loss of capillary bed except by occasional cardiac catheterization.

As equipment became available, more pulmonary function tests were added to the study. At the present time each patient receives spirographic determination of vital capacity (VC) and maximal breathing capacity (MBC). Timed vital capacity (TVC) determinations are made on a Collins vitalometer fitted with a potentiometer to obtain a time volume graph on a Sanborn recorder (7). In patients who reveal grossly abnormal findings, functional residual capacity determinations (FRC) are made by a modified Darling open-circuit technique, monitoring the test with a Waters Conley nitrogen meter (8). This allows a more accurate determination of the index of intrapulmonary mixing than the Haldane alveolar sampling technique. Each patient receives a single breath of oxygen and the alveolar nitrogen curve is analyzed according to the technique of Comroe and Fowler (9). Whenever indicated, differential bronchospirometry is performed and the alveolar nitrogen curve is obtained from each lung separately (10).

OBSERVATIONS

Three hundred and twenty-eight consecutive patients with an average age of thirty-seven years have been studied in this laboratory and have undergone thoracic surgery. All but 3 patients yielded pulmonary tissue of sufficient amount for examination. One of the exceptions was a patient who had a decortication of thick bony pleura; the other 2 had emphysema and so much disease that resection was thought to be unwise. Bilateral resection was performed in 56 patients. Two hundred and ninety-five patients had proved pulmonary tuberculosis, 4 had carcinoma, 2 had pulmonary fibrosis, 2 had undiagnosed granuloma, one had a calcified pleural plaque, and one had bronchiectasis. The remaining 23 patients were not proved to have tuberculosis by bacteriologic studies, but the histopathologic findings were compatible with this diagnosis.

Of the 328 patients, 150 were found to have significant emphysema at the time of operation or on gross examination of the resected specimens. The preoperative

mal breathing capacity, 69 per cent, with elevated spirogram; single breath of oxygen, 3 per cent; residual air/total capacity × 100—20 per cent; index of intrapulmonary mixing, 3.5 per cent.

Left—right upper lobe

Right—apico-posterior segment, left upper lobe.

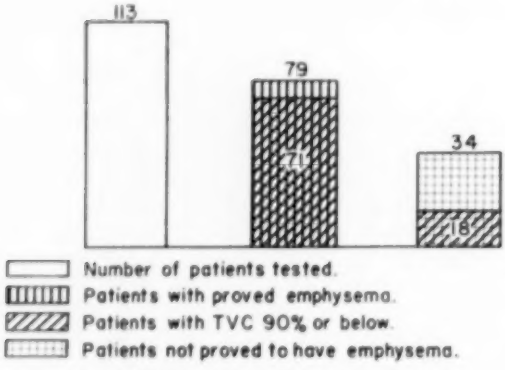

FIG. 3. Timed vital capacity—two-second

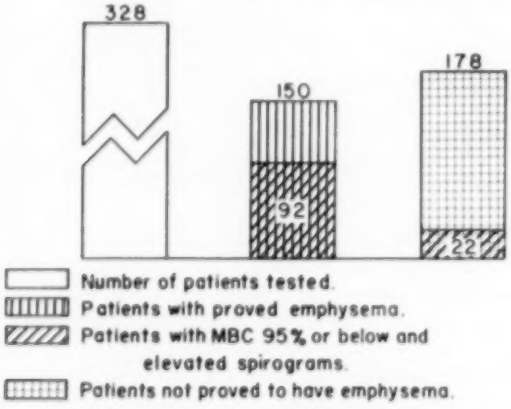

FIG. 4. Maximal breathing capacity

vital capacity performed on all of these emphysematous patients showed no diagnostic pattern except that a prolongation of the expiration on the spirogram was usually present. One hundred and thirteen patients were studied with the more sensitive timed vital capacity method, using the vitalometer (figure 3). Of these, 79 had emphysema proved by resection. Seventy-one of the emphysematous patients had two-second timed vital capacity of 90 per cent or less. Eighteen had abnormal timed vital capacity without the finding of emphysema. The use of Gaensler's normal value of 94 per cent for two-second timed vital capacity increased the number of false positives considerably.

All of the 328 patients had maximal breathing capacity tests (figure 4). The MBC was considered abnormal when the volume was 95 per cent or below the predicted value and elevation of the spirogram showed air trapping. Elevation is an important feature and must be present except in the occasional patient who has such a low inspiration capacity that elevation cannot be attained. Ninety-two

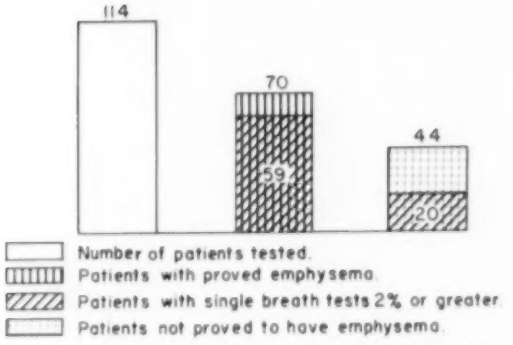

FIG. 5. Expiratory nitrogen curve after single breath of oxygen

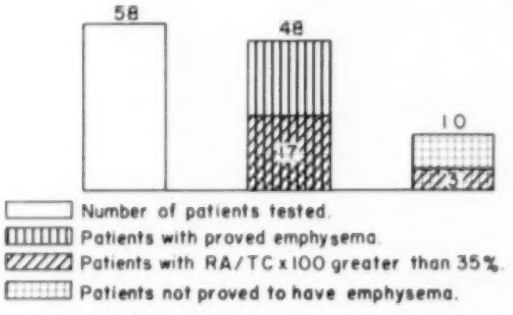

FIG. 6. Ratio of residual air/total capacity × 100

emphysematous patients had reduced MBC and elevated spirograms. In addition there were a number who had somewhat higher MBC values and elevation of the spirogram. When the nitrogen meter became available, if such patients showed in addition a rising curve of alveolar nitrogen after a single breath of oxygen, emphysema was usually present. There were 22 patients with abnormal MBC and elevation of the spirogram in whom emphysema was not demonstrated.

The single breath of oxygen test was performed on 114 patients (figure 5). Seventy of these patients had proved emphysema. Fifty-nine of the latter had 2 per cent or more rise in the alveolar nitrogen curve. There were 20 patients with abnormal nitrogen curves in whom emphysema was not demonstrated. Many of them had bronchiectasis or cavitary disease. These conditions or bullae communicating with bronchi may be suspected when a terminal rise appears in the curve.

When the MBC and TVC were grossly altered, functional residual capacity studies were frequently carried out. Fifty-eight of the patients had the seven-minute nitrogen washout test (figure 6). Forty-eight of these patients had proved emphysema. Only 17 patients of this group had a ratio of residual air/total capacity × 100 greater than 35 per cent. These patients all had severe degrees of

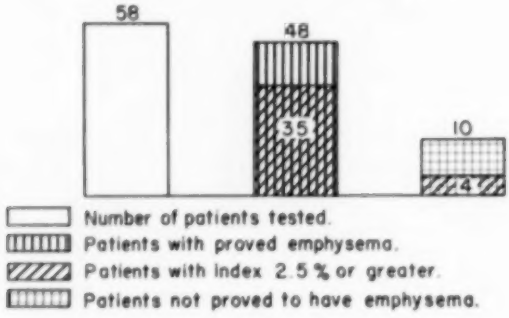

FIG. 7. Index of intrapulmonary mixing

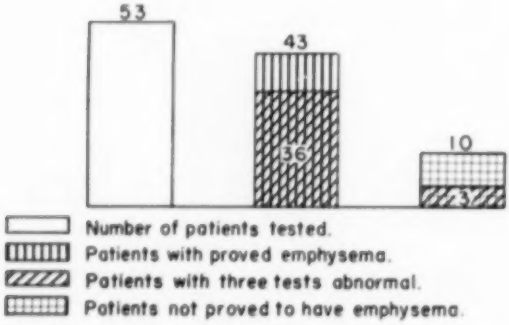

FIG. 8. Combination of three tests: timed vital capacity, maximal breathing capacity, and single breath of oxygen.

emphysema, as seen in the gross specimens. Three patients had a ratio greater than 35 per cent without the findings of emphysema, but their resections were small and did not give a representative portion of lung tissue.

Forty-eight emphysematous patients likewise had determination of the index of intrapulmonary mixing after breathing 99.4 per cent oxygen for seven minutes (figure 7). Thirty-five of them had indices of 2.5 per cent or greater. Four patients with abnormal indices were not shown to have emphysema.

Finally, 53 patients were tested by a combination of TVC, MBC, and the single breath of oxygen test (figure 8). In this group the timed vital capacity was considered abnormal if the two-second percentage was 90 per cent or less. An elevation of the spirogram in the MBC test was considered abnormal with or without reduction in MBC. The criterion for abnormal single breath of oxygen was 2 per cent or greater. Forty-three patients were shown to have emphysema. Of these, 36 had abnormal findings in all of the tests. Three had abnormal tests without proof of emphysema. One of the 3 patients had a fibrotic atelectatic right upper lobe removed and 2 had bronchiectatic lobes removed from under old thoracoplasties.

DISCUSSION

The group evaluated by the combination of the three tests (timed vital capacity, maximal breathing capacity, and single breath of oxygen) was composed of patients who had more disease than those processed early in the study; hence a higher proportion of detectable emphysema was found. Furthermore, in this group, reduction of MBC was not considered, but elevation of the spirogram to hyperinflation level was used in conjunction with the abnormal single breath of oxygen test. This brought 6 patients into the emphysematous group who would have been excluded if the criterion of 95 per cent or lower were used for abnormal MBC. By the last-named manuever, only one false positive diagnosis was introduced.

If each test in the group of patients in the present study is compared with the others, the timed vital capacity has the best score. By its use 4 patients with emphysema were overlooked and 5 so-called false positive diagnoses were added. The timed vital capacity, the maximal breathing capacity, and the single breath of oxygen tests measure somewhat different functions of the lung and, therefore, in combination tend to exclude false positive findings. When all three tests are abnormal, it becomes more certain that anatomically significant emphysema is present.

SUMMARY

Pulmonary resection of 328 patients provided a unique opportunity to determine the presence of pulmonary emphysema. Preoperative pulmonary function tests were correlated with 150 patients who had varying degrees of proved emphysema. The ratio of residual air/total capacity × 100 was greater than 35 per cent in only 17 severely emphysematous patients and failed to indicate emphysema in the early stages. A combination of prolonged timed vital capacity, maximal breathing capacity spirogram elevated to hyperinflation level, and a rising curve of alveolar nitrogen after a single breath of oxygen provided a sensitive indication of early emphysema.

SUMARIO

Descubrimiento del Enfisema Pulmonar Incipiente

La ejecución de la resección pulmonar en 328 enfermos proporcionó una oportunidad extraordinaria para determinar la presencia de enfisema pulmonar. Las pruebas preoperatorias de la función pulmonar se correlacionaron con las de 150 sujetos que tenían enfisema comprobado más o menos grave. La proporción de aire residual/capacidad total × 100 sólo excedió de 35 por ciento en 17 enfisematosos graves, sin que indicara enfisema cuando éste se hallaba en las etapas incipientes. Una combinación de la capacidad vital prolongada, una capacidad respiratoria máxima en el espirograma elevada al nivel de la hiperinflación y una curva ascendente del nitrógeno alveolar después de una sola aspiración de oxígeno ofreció una indicación sensible del enfisema incipiente.

RESUME

Détection de l'emphysème pulmonaire au début

L'exérèse pulmonaire pratiquée chez 328 malades a procuré une occasion unique de déterminer la présence d'emphysème pulmonaire. Dans 150 cas, une corrélation a été établie

entre les tests préopératoires de la fonction pulmonaire et divers degrés d'emphysème pulmonaire confirmé. Le rapport air résiduel/capacité totale × 100 n'a dépassé 35% que dans 17 cas d'emphysème sévère et n'a pas décelé l'emphysème au stade initial. Une combinaison de capacité vitale de temps prolongé, de spirogramme de la capacité respiratoire maxima élevée au degré d'hyperinflation et une courbe croissante de l'azote alvéolaire succédant à une seule inhalation d'oxygène constituaient un indice sensible de l'emphysème au début.

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TISSUE CULTURE ANALYSIS OF TUBERCULIN HYPERSENSITIVITY IN MAN[1,2,3]

E. F. O'NEILL AND C. B. FAVOUR[4]

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INTRODUCTION

The delayed type of tissue response to the products of an infecting organism was first described by Jenner (1) in his study on vaccination for smallpox. It did not receive wide attention until Koch (2) pointed out the difference between the primary lesions of tuberculosis, in which bacterial invasion takes place with little injury to the host tissues, and the later lesions which are complicated by an intense allergic response to proteins derived from the tubercle bacillus. Since that time, this allergic response has come to be known as the tuberculin-type reaction. It is also called bacterial hypersensitivity because many bacterial infections are accompanied by a similar specific sensitization to antigens of the infecting organism. This type of reaction is not, however, confined to bacterial infections. Drug therapy and infections caused by viruses, fungi, and parasites may also induce delayed-type hypersensitive responses.

Of the many laboratory tools which have been used to study the tuberculin reaction, tissue culture and other *in vitro* methods using experimental animals have received wide attention. The majority of these investigations have been on experimental animals. The present study was designed to confirm and extend these observations in human subjects with clinical tuberculosis. This was done by determining the toxicity of tuberculin by measuring its effect on the migration of peripheral blood leukocytes cultured in capillary tubes. Since there have been many recent additions to the literature on the *in vitro* effect of tuberculin on cells, these new data are introduced by a brief historical review.

Historical Review

One of the earliest tissue culture studies on tuberculin hypersensitivity was made by Holst (3) who observed that the migration of leukocytes from tuberculin-sensitive persons was decreased in the presence of tuberculin. He also noticed that the ability of such leukocytes to phagocytose bacteria was likewise decreased. Renewed interest in tissue culture methods for studying tuberculin hypersensitivity followed the work of Rich and

[1] From the Tuberculosis Research Laboratory, Veterans Administration Hospital, Rutland Heights, Massachusetts; the Medical Clinics of the Peter Bent Brigham Hospital, Boston, Massachusetts; and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director.

[3] This investigation was supported by United States Public Health Service grants Nos. H-1074, E-32, and E-941.

[4] Present address: The Palo Alto Medical Research Foundation, Palo Alto, California, where work on this study was completed.

Lewis (4, 5) and the development of the concept, well presented in Rich's book (6), that immunity in tuberculosis is independent of hypersensitivity. Rich and Lewis give data on representative tissue cultures of blood leukocytes (buffy coat), spleen cells, and bone marrow cells, maintained in either autologous or normal plasma coagulums containing 1:60 Old Tuberculin (OT). They observed that adding tuberculin to the cells from a sensitized animal regularly caused altered morphology and that cell migration ceased after an initial period of normal migration.

Aronson (7), who soon repeated this work, and reported representative experiments, found that tuberculins from human and bovine strains of tubercle bacilli produced toxic effects on cells from tuberculous guinea pigs. In addition, he found that cells from an animal anaphylactically sensitized to horse serum were not injured by horse serum in the tissue culture fluid. Moen and Swift (8) and Moen (9) extended this work to streptococcal infections in guinea pigs. They found that tissue culture sensitivity was disease specific by exposing cultures from tuberculous and *Streptococcus*-infected guinea pigs to tuberculin and to a streptococcal protein. Heilman and Seibert (10), Heilman, Feldman, and Mann (11), and Fabrizio (12) have likewise reported tissue culture experiments demonstrating the toxicity of tuberculin for cells of tuberculin-sensitive animals. Fabrizio pointed out, as did Rich and Lewis (4), that very large amounts of tuberculin were necessary for this tissue culture effect. Neither polysaccharides nor nucleic acids from tubercle bacilli had a toxic effect in tissue cultures (10, 12).

Another facet of the cytotoxic effect of tuberculin on sensitized cells was explored by Heilman and Seibert (10) who studied the effects of tuberculin on various cell types in their tissue cultures. They found that lymphocytes seemed to be least injured by tuberculin, neutrophils were most easily injured, and monocytes were injured in cultures held for longer periods of time. These were qualitative observations made on the cells at the periphery of the zone of migration. Further comment on the toxic effect of tuberculin for specific cell types will be made later in this summary.

Not all workers who have studied the toxic effect of tuberculin on cells have obtained results that are in close agreement with those of the workers mentioned above. An impressive number of careful efforts to demonstrate the specific toxic effect of tuberculin *in vitro* for cells of tuberculin-hypersensitive subjects have yielded negative or equivocal results.

Fischer (13), working with twelfth-passage explants of fibroblasts from a chicken infected with avian tubercle bacilli, found that these cells were not sensitive to avian tuberculin. Stimulation by tuberculin of tissue culture migration was noted by Juhasz-Schaffer (14). He used first-passage tissue cultures of kidney explants from tuberculin-sensitive guinea pigs. The cultures were grown in 1:1 dilutions of autologous plasma in salt solution. The open end of a capillary tube containing OT, 1:1,000 to 1:2,000, was placed in the plasma coagulum which held the tissue culture in place. Under these conditions, stimulation of cell migration by the small amounts of tuberculin which diffused into the cell mass was probably the result of subtoxic concentrations of tuberculin for this particular cell system.

Baldridge and Kligman (15) used bone marrow and splenic tissue cultures from guinea pigs infected with virulent tubercle bacilli. Their experiments were done in a manner quite similar to that used by Rich and Lewis except that they used human serum instead of homologous animal serum. High concentrations of both OT and purified protein derivative (PPD-S) were nontoxic for their tissue cultures. Jacobi and Marks (16) used first explantations of hepatic and renal epithelial cells from tuberculin-sensitive guinea pigs. They found no toxic effects of tuberculin on their tissue cultures when the explants were

grown either in autologous or in homologous plasma. Cruickshank (17) grew dermal explants from sensitized guinea pigs in media containing autologous plasma and very large amounts of tuberculin. No toxic effect was noted.

Jacobi and Marks (16) have suggested that cells of epithelial origin may not be affected by tuberculin, whereas cells of mesenchymal origin are. These authors further suggest that the reason Buckley, Buckley, and Keeve (18) were able to show a cytotoxic effect of tuberculin on liver explants was that the latter group was working with cells which were predominantly fibroblasts.

Warburg respiratory studies have not shown a specific toxic effect of tuberculin on cells of hypersensitive subjects. Marks and James (19) studied the oxygen consumption of peritoneal exudate cells consisting of 95 per cent neutrophilic leukocytes. These cells were derived from tuberculin-sensitive guinea pigs and were exposed *in vitro* to large amounts of tuberculin. No effect on oxygen consumption was noted. Sanford and Favour (20) have repeated this type of Warburg study, using peripheral blood lymphocytes and suspensions of splenic cells. Each of these types of cell suspension was from guinea pigs inoculated with BCG. No inhibition of oxygen consumption was observed in the presence of either OT or PPD-S. It is apparent that measurement of oxygen consumption by cells is a relatively insensitive method for detecting the toxic action of tuberculin. Kerby and Chandhuri (21) have recently reported a study in which evidence of cell damage *in vitro* by tuberculin was sought by measuring the amount of lysozyme released by leukocytes. Tuberculin caused no increase in the rate of lysozyme release from hypersensitive cells incubated *in vitro* with tuberculin.

The studies on tuberculin allergy *in vitro* reviewed above have indicated that cells taken from a sensitized host sometimes do and sometimes do not undergo specific injury in the presence of tuberculin. One explanation for these different results may be the degree to which a given cell preparation is freed of autologous plasma factors which themselves influence the tuberculin reaction. Studies by Wells and Wylie (22) on the plasma of patients with sarcoid and certain other disease states indicate that at times plasma may contain a tuberculin neutralizing factor. As will be seen, at other times plasma may contain a sensitizing substance which brings about specific cell damage in the presence of tuberculin. Cell adsorption or cell trapping of plasma is not an easy condition to avoid in tissue culture experiments. First-passage tissue cultures might be expected to retain plasma and to show either the presence or the absence of specific tuberculin sensitivity. This variability already has been mentioned. In contrast, twelfth-passage tissue cultures which have undergone a considerable diluting out of any retained plasma might be expected to be insensitive to tuberculin, as was the case in Fischer's experiments (13). Third-passage cultures might be expected to retain sensitivity to tuberculin, which they do (5, 8).

The existence of a plasma factor which mediates tuberculin toxicity has been suspected for a long time. Zinsser and Mueller (23) had occasional successes in passively transferring tuberculin allergy to a normal animal with the serum of a sensitized animal. Rich and Lewis (5) observed that in some instances the tissues of normal animals appeared to be somewhat more sensitive to tuberculin in the presence of plasma from sensitized animals than in the presence of plasma from normal animals. Kirchheimer and Weisser (24) concluded that the close similarities between the development of hypersensitivity of the tuberculin type and that of anaphylactic allergy, in which a circulating plasma factor readily can be demonstrated, points to the probability that a plasma factor likewise is involved in tuberculin-type hypersensitivity.

Recently Cole and Favour (25) have described a plasma factor found in fraction IV-10 of the plasma of sensitized guinea pigs which will passively transfer a delayed reaction to

tuberculin to normal animals. These reactions are maximal in less than forty-eight hours, much like those to be described which are transferred with cells (26, 29, 30). Necrosis is not a feature, as is the case of some (26) but not all (29, 30, 31), of the delayed reactions transferred by cells.

Another explanation for the finding by some tissue culture workers of a positive, and by others of a negative, effect of tuberculin *in vitro* is the presence or absence in a given cell population of certain cells capable of sensitizing other cells present. Chase (26) has shown that tuberculin hypersensitivity can be passively transferred to normal guinea pigs by injecting them with suspensions of washed peritoneal exudates containing a predominance of mononuclear cells from hypersensitive animals. Cummings, Hoyt, and Gottschall (27) and Kirchheimer and Weisser (24, 28) confirmed Chase's results with guinea pigs, while Lawrence (29) and, more recently, Good (30) have shown that transfer of tuberculin hypersensitivity can be accomplished in human beings either by leukocytes or by constituents of disrupted leukocytes (31). Kirchheimer, Hess, and Spears (32), working with guinea pigs, obtained positive results in passive transfer experiments, using mononuclear cell suspensions similar to those used by Chase, but obtained negative results with suspensions consisting almost exclusively of granulocytes.

Other evidence that there is, in the plasma of the hypersensitive animal, a factor which mediates the specific cytotoxic action of tuberculin, has been advanced by several groups utilizing the cytolysis procedure of Favour (33) and his associates. These workers found that the presence of tuberculin in suspensions of cells from selected tuberculin-sensitive donors will cause lysis of a portion of the cells within an hour. Miller, Vaughan, and Favour (34) found that this specific lytic action of tuberculin required complement, while Miller and Favour (35) showed that lymphocytes from tuberculin-sensitive guinea pigs released into the plasma a substance which sensitized normal guinea pigs' cells to tuberculin. They also showed that neutrophils did not release this plasma factor, nor were they injured by tuberculin unless either lymphocytes or plasma factor were present. This prompt lytic effect of tuberculin on a portion of the cells derived from various parts of the tuberculous host has been observed by numerous workers. Wesslén (36) showed the toxic effect of tuberculin for thoracic duct lymphocytes of tuberculin-sensitive rabbits; Kanzler (37), for cells in the urine sediment from subjects with renal tuberculosis; and Waksman (38), for the peripheral blood cells of rabbits with tuberculosis. The cytolysis technique has also been used in a similar fashion by Chamberlin for the study of cell sensitivity to streptococcal infections (39).

It is clear that there are many reasons for the success or failure of any *in vitro* study of tuberculin hypersensitivity. A tissue culture preparation containing some cells of the type which mediate the passive transfer of tuberculin allergy in the whole host might be expected to be sensitive to tuberculin. When this culture is subdivided many times, it still may contain enough of these cell types to sensitize the remainder of the tissue culture.

On the other hand, the work with the cytolysis technique suggests that, in addition to the role played by special cells, tissue injury by tuberculin is also mediated by a humoral factor shed by lymphoid cells. A tissue culture system which is not thoroughly washed free of plasma or which contains lymphocytes may appear to be inherently sensitive to tuberculin. A tissue culture system made up of either neutrophils or epithelial cells or even of mononuclear reticulo-endothelial cells from regions of the body not affected by a tuberculous process might be expected to be resistant to tuberculin.

With due recognition of these possible technical pitfalls, the present study was started in an attempt to measure the toxicity of tuberculin for the cells of both tuberculous and nontuberculous human subjects.

MATERIALS AND METHODS

In the present study, a capillary tube procedure somewhat similar to the one employed by Holst (3) has been used. This method measures migration of leukocytes from the layer of white cells which forms as a "buffy coat" over the packed erythrocyte mass in capillary tubes when the tube is centrifuged. Leukocytes normally migrate actively along available surfaces provided by tube walls and the fibrils of plasma clots.

With this method, the toxic action of tuberculin is manifest as inhibition of the normal tendency of leukocytes to migrate. Inhibition is measured by means of a cytotoxic index of migration in the presence of tuberculin divided by the distance of migration in the absence of tuberculin.

This method was used in preference to *in vitro* techniques employing tissue explants cut from buffy coats because of its greater simplicity. With it, cells can be washed reasonably free of autologous plasma, uniform numbers and types of cells can be placed in each culture, multiple cultures can be done to permit statistical treatment of results, and only one radius of migration need be measured, namely that along the axis of the capillary tube.

Clinical Material

The method described above was used on materials derived from three groups of persons: tuberculous subjects, tuberculin-positive healthy subjects, and tuberculin-negative healthy subjects. Data on the cutaneous reactivity of these persons to tuberculin and to other bacterial products, which were used for control antigens in the tissue cultures, are given in table 1. The three groups are described more fully below.

Tuberculous subjects: The 21 persons in the tuberculous group were men who were hospitalized for chronic pulmonary tuberculosis. One, T-11, was a Negro. Their ages ranged from twenty-one to fifty-five years, the majority being between twenty and thirty-five years of age. By National Tuberculosis Association standards, 13 had moderately advanced, and the rest had far advanced, pulmonary tuberculosis. Two patients, T-9 and T-13, who had had active tuberculosis in the past, had inactive lesions and sputum cultures negative for tubercle bacilli while they were a part of this study. The others had active tuberculosis and were discharging culturable tubercle bacilli in the sputum. In some, the disease was of less than a year's duration at the time of hospitalization when they were admitted to the study. In others, the disease had been present for a variable number of years, appearing in recurrently active episodes. Most of the patients had had antimicrobial therapy in the past with indifferent long-term results. Various types of medical and surgical therapy had produced temporary remissions. All patients studied had positive cutaneous reactions to first (0.02 γ) or intermediate (0.2 γ) PPD-S.

Tuberculin-positive healthy subjects: This group consisted of hospital personnel having a positive skin test to first (0.02 γ), intermediate (0.2 γ), or second strength (5 γ), PPD-S. None of these persons was known to have had clinical tuberculosis. All were considered to be in good health on the basis of physical examination and one or more chest roentgenograms during the course of this investigation. Two subjects (P-9 and P-18) were classified as tuberculin-positive reactors although most of the time their reaction to second-strength PPD-S was either negative or doubtful. Other subjects whose skin tests were consistently positive also showed moderate fluctuations in the degree of their reactivity to tuberculin.

Tuberculin-negative healthy subjects: This group consisted of healthy hospital personnel whose intracutaneous tuberculin tests were consistently negative when classified according to the criteria outlined in *Diagnostic Standards and Classifications of Tuberculosis* (40). Skin tests on two subjects (N-3 and N-6) showed on two or more occasions induration of more than 5 mm. in diameter at twenty-four hours. This induration disappeared

TABLE 1
CUTANEOUS REACTIONS* TO TUBERCULIN PPD-S, BRUCELLERGEN®, AND "STREPTOCOCCUS 98"

Subject	First Strength 2×10^{-5} mg.	PPD-S Intermediate Strength 2×10^{-4} mg.	Second Strength 5×10^{-4} mg.	Brucellergen® 0.01 mg.	"Streptococcus 98"	
					0.01 mg.	0.1 mg.
N 1†	0	0	0			
2	0	0	0	0	+	++
3	0	0	0	++	++	++
4	0	0	0	+++	+++	++++
5	0	0	0	+++	0	+++
6	0	0	0	0	+	
7	0	0	0		+	
P 1†	+		+++	+	+	++
2	0		++	0	+	
3	0	0	+++	0	+	++
4	+++			+	++	+++
5	+			0	+++	
6	+++			+	++	+++
7	+			0	++	
8	+++			+++	+	+++
9	0	0	+	0	+	+++
10	0	0	+	+	++	
11	+			0	+++	
12	+			++++	++	
13	+++			+	+	
14	++			++++	++	
15	0	++		0	+++	
16	+					
17	0	0	+	0	+++	++
18	0	0	+	0	+	++
19	0	0	+++			
20	+			++	+	+++
21	++			+++	0	++
T 1†	++			0	+	
2	+					
3	0	+		0	+	++
4	+			0	+	
5	0	+		0	0	++
6	+					
7	+			0	++++	
8	+++			0	+	++
9	+					
10	++			+	+	+
11	+			+	+	++
12	++			0	+	
13	0	+				
14	++			+	+	++
15	++			0	+	
16	++			0	0	+++
17	++			++	+	
18	+			+++	+	
19	++			0	++	
20	+			++	+	
21	+			+	+++	

* Criteria for the reading of skin tests in + marks are those in common use for PPD.
† N, normal subjects with negative tuberculin reactions; P, normal subjects with positive tuberculin reactions; T, patients.

by forty-eight hours. Although these responses were definite reactions to tuberculin, these persons, nevertheless, were included in the tuberculin-negative group in conformity with accepted criteria for the interpretation of skin tests.

Antigens

Tuberculin: For *in vitro* tests a single large lot of tuberculin was prepared from the unheated Seitz-filtered supernatant of a seven-week culture of H37Rv tubercle bacilli grown on a synthetic mass culture medium (41). The filtrate was dialyzed at 4°C. for forty-eight hours against multiple changes of distilled water. An aliquot of the pooled material was then lyophilized to a dry powder to determine the volume-to-dry-weight ratio. On the basis of this value, the remainder of the lot was dispensed aseptically into tared ampules so that each would contain 25 mg. of tuberculin. These were then lyophilized and sealed in an atmosphere of helium somewhat below atmospheric pressure and stored at −15°C.

When the dry powder was taken up in saline for intradermal testing, it was found to have approximately one-third the biologic potency by weight of commercial PPD-S. This assay was done by matching the sizes of cutaneous reactions produced by serial dilutions of the two tuberculins. Guinea pigs, sensitized to tuberculin by multiple injections of heat-killed H37Rv tubercle bacilli suspended in mineral oil, were used for the assay. Normal animals showed nonspecific reactions to 10 mg. but not to 0.1 mg. of this H37Rv tuberculin.

This material was used in preference to either OT or PPD-S. The single large lot made possible uniformity of material throughout the protracted course of this study. Both OT and PPD-S proved to be generally satisfactory in preliminary tests. Neither was used, however, because different lots of these materials which were available commercially varied in the range between their specific and nonspecific *in vitro* cytotoxicity.

Streptococcal antigen: Cultures of Group A, β-hemolytic streptococcus number 98[5] were grown in 100 ml. lots of a tryptic digest broth to which the organism had been adapted. Thirty-six hour growths were washed three times by centrifugation from phosphate buffered saline at pH 7.3, resuspended in saline containing 50 mg. per 100 ml. carboxylmethoxylamine hemihydrochloride as preservative (42), heated at 60°C. for one hour, and stored at 4° to 8°C. Sterility was checked with 1 ml. aliquots incubated in thioglycolate broth for forty-eight hours at 37°C.

The density of the suspension was adjusted with a barium standard to approximately 900,000,000 organisms per ml. One-tenth milliliter amounts of this material when diluted as much as 1:1,000 with saline solution (0.001 mg. nitrogen per 0.1 ml.) produced typical delayed type cutaneous reactions in subjects with known β-hemolytic streptococcal infections. Normal subjects showed various reactions to this material (table 1).

Tissue cultures were set up with varying concentrations of streptococcal antigen. The streptococcal material was an excellent control antigen for the purposes of this type of study. It was capable of eliciting a delayed type cutaneous reaction similar to that produced by tuberculin. In addition, many tuberculous patients showed varying degrees of sensitivity to it. A soluble antigen obtained from the streptococcus with similar properties was used by Moen and Swift (8) in a tissue culture study which used both antigen and disease controls.

Brucella antigen: Brucellergen[5,6] (43) also served as a control antigen. It was used for intradermal tests in the standard dosage (0.1 ml. containing approximately 1/10,000 brucella protein nucleate). This material was chosen because, like tuberculin and the streptococcal antigen control, it is capable of producing delayed allergic reactions in specifically hypersensitive subjects.

Avian tuberculin: Early in the course of the present experiments, it was thought that tuberculin prepared from avian tubercle bacilli might be satisfactory as a control antigen for the human tissue culture work. Accordingly, avian tuberculin was prepared from media

[5] A laboratory strain of Group A, β-hemolytic streptococcus used for penicillin assay and the preparation of skin-testing antigen.

[6] Brucellergen Protein Nucleate, manufactured by Sharp and Dohme.

filtrate, using the procedure outlined for H37Rv tuberculin. When tested in guinea pigs sensitized with heat-killed H37Rv, it was found that, although its potency was one fiftieth that of H37Rv tuberculin, the avian tuberculin caused cutaneous reactions grossly indistinguishable from those produced by H37Rv tuberculin. Furthermore, tissue cultures of human leukocytes reacted to avian tuberculin in the same way that they did to H37Rv tuberculin when biologically equivalent quantities[7] were used. The avian tuberculin was not studied further. It appeared to differ from H37Rv tuberculin only quantitatively in specific potency and to be approximately equal to H37Rv tuberculin in nonspecific toxicity.

General Method of Experimentation

Two series of experiments provided the data of the present report. In the first series, leukocytes from the three groups of test subjects were washed and suspended in autologous plasma containing varying concentrations of tuberculin and control antigens. In the second series of experiments, leukocytes from the three groups of subjects were washed and suspended in homologous plasma[8] containing that concentration of tuberculin found to be most critical in the first series of experiments. The second group was divided into two subgroups. In both of these, the type of plasma used to suspend cells rather than the amount of antigen was the variable. In the first subgroup, the cells and plasma of patients and normal controls were exchanged. In the second subgroup, the cells and plasma of patients and tuberculin-positive normal subjects were exchanged.

Preparation of capillary tube cultures: Subjects were bled from an anticubital vein into a 20 ml. syringe. Syringes and all other glassware used in processing blood or cell suspensions, with the exception of capillary tubes, were coated with silicone.[9] The blood was discharged into two 15 ml. pointed centrifuge tubes containing sufficient heparin[10] solution to give a concentration of 0.1 mg. per ml. of blood. One tube, containing 13 ml., was centrifuged at 4°C. at 1,500 G (3,000 r.p.m.) for fifteen minutes and the plasma was decanted into a second centrifuge tube. This plasma was then recentrifuged at the same speed and decanted into a third tube which was stoppered and stored at 8°C. for use later in the experiment.

The second tube, containing 7 ml. of blood, was equilibrated with an equal volume of Hanks' balanced salt solution (44) and centrifuged in the cold at 120 G (800 r.p.m.) for fifteen minutes, or until the cell boundary was well down in the tube. The supernatant fluid, containing most of the blood platelets, was removed with a capillary pipette and discarded. The cells were then suspended in 14 ml. of Hanks' solution, recentrifuged at 120 G, and the supernatant discarded. This washing process was repeated twice. Usually 5 to 6 ml. of cells in fluid remained in the tube following removal of the supernatant. Just before this remaining material was used to prepare the final cell suspension, it was mixed by pipetting.

Basic protocol for both experimental series: Cells, plasma, and antigen were then combined in varying proportions as indicated in the sample protocol (table 2). The master tubes were shaken at 300 to 400 times a minute to disperse the cells, and from these a series of small glass tubes[11] 7 cm. long with an internal diameter of 0.6 plus-minus 0.1 mm. were filled to two-thirds of their length by capillary action. The empty end was heat-sealed in the flame of a high temperature microburner and quickly cooled by immersion in cold alcohol.[12] Usually 6 to 10 replicates were prepared from each master tube. Each group of

[7] Avian tuberculin was assayed in sensitized guinea pigs in the same manner as that used for H37Rv tuberculin.

[8] Subjects of the same blood type by erythrocyte A, B, O, and Rh antigens.

[9] Dryfilm 2087—General Electric Company.

[10] Liquaemine®, manufactured by Organon, Inc., Orange, New Jersey.

[11] Capillary tubing supplied for clotting time determination from several commercial sources has proved satisfactory.

[12] Cooling in water will often fracture the capillary tube.

TABLE 2

EXAMPLE PROTOCOL, AUTOLOGOUS CELL PLASMA STUDIES

Subject: N 2

Date: September 22, 1952

Diagnosis: Tuberculin negative normal, type O, Rh positive

	H37Rv Tuberculin				"Streptococcus 98"			Saline Control
Initial antigen concentration: (mg/ml)	5.0	2.5	0.5	0.05	1.0	0.5	0.2	
Cells (ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Plasma (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Tuberculin (ml)	0.2	0.2	0.2	0.2				
"Streptococcus 98" (ml)					0.2	0.2	0.2	
Saline (ml)								0.2
Final antigen concentration: (mg/ml)	1.0	0.5	0.1	0.01*	0.2	0.1	0.04	—
Capillary tube (migration in mm)								
1	2.3	1.6	2.6	2.6	1.6	2.7	2.2	2.5
2	2.0	2.6	1.9	3.0	1.9	2.8	3.0	2.5
3	1.9	2.3	2.7	2.3	1.4	2.5	2.7	1.7
4	1.4	2.5	1.8	3.1	2.1	1.7	1.8	2.5
5	1.4	1.8	2.7	2.2	2.3	2.3	2.2	1.9
6	1.2	2.4	2.1	2.3	1.3	1.9	1.8	3.2
7	1.9	2.1			1.5			
Average migration (mm)	1.73	2.20	2.30	2.58	1.73	2.31	2.28	2.38
Cytotoxic index†	0.73	0.93	0.97	1.07	0.73	0.97	0.96	

* 0.01 mg. of H37Rv tuberculin is approximately equivalent to 0.003 mg. of PPD-S, or slightly less than the standard second-strength skin test dose of 0.005 mg. The values for control antigen are in mg. per ml.

† Cytotoxic indices are obtained by dividing the average migration in each antigen concentration by the average migration in saline control tubes.

tubes was centrifuged in the cold at 1,500 G for ninety seconds. Hematocrits on these capillary tube preparations were in the range of 25 per cent plus minus 5 per cent. The lack of a large platelet plaque, made possible by the cell washing procedure, provided a free path for leukocyte migration as well as optimal conditions for oxygen and carbon dioxide transport and for cell nutrition. This is a factor of some importance because platelets, which make up much of the buffy coat in a conventional hematocrit, have a considerable *in vitro* oxygen consumption (45).

Following centrifugation, capillary tubes were inspected microscopically to make certain that a sharp cell-plasma interface had been obtained and that the tube walls were essentially free of adherent leukocytes. Tubes were then incubated overnight at 37°C. in a vertical position. The following morning, each group of replicate tubes was mounted on a 1- by 3-inch microscopic slide with Duco cement, placed at the opposite end of the tubes from those being studied, and the distance of leukocyte migration measured with a mechanical stage vernier. The furthest distance to which the circumference of the capillary tube was covered by an even sheet of cells was selected as the end point of migration.

The heparin concentration used was 0.1 ml. per 10 ml. in all the original tubes of blood throughout this study. Usually this amount of heparin prevented a clot from forming until after the migration readings were made at sixteen hours. Clots which did form during the period of incubation consisted of a loose fibrin web. Preliminary experiments using vary-

ing concentrations of heparin in the final cell suspensions indicated that a firm clot tended to displace the plasma-cell interface. This displacement made it difficult to measure migration accurately. A loose clot or no clot did not interfere with migration.

An internal tube diameter of 0.7 mm. was found to be the size above which the erythrocyte mass was frequently displaced by gravity while tubes were lying horizontally on the microscope stage for the short time during measurement determination. The packed erythrocyte mass, in tubes of 0.7 mm. or less in internal diameter, retained a sharp boundary for five to ten minutes while measurements were being made. A diameter range of 0.6 mm. plus-minus 0.1 mm. was chosen to give reproducible results in this experimental procedure.

Cytotoxic index of cell migration: It was found difficult to quantitate other toxic properties of tuberculin, such as the effect on different cell types, the amount of pyknosis, or the degree of hemoglobin reduction. Although it appeared that cell functions other than linear migration were altered by specific as well as by nonspecific influence, these changes did not lend themselves to mathematical treatment. Because granulocytes move fastest and farthest in these tubes, the results observed represent primarily the toxic effect of the plasma antigen system on granulocytes.

Comparison of leukocytic migration distances with and without either tuberculin or control antigens in the system was made with a cytotoxic index (table 2). A similar cytotoxic index has been used by others who have studied tuberculin toxicity in tissue cultures (8, 10, 13). It was noted that some cell migration from the buffy coat occurred before either specific or nonspecific toxic effects began. By one hour, migration had ceased in those tubes with a low cytotoxic index. Migration continued at a slower rate for longer periods in cell systems in which there was less toxicity.

OBSERVATIONS

Series I. The Effect of Varying Concentrations of Tuberculin on Cells in Autologous Plasma

The effect of varied concentrations of tuberculin on cells in autologous plasma was studied according to the protocol described above (table 2).

The three study groups of subjects consisted of tuberculous patients and the two control groups. These served as donors of the plasma-cell systems which were exposed to tuberculin and control antigens. The cells from each subject were exposed to three or more concentrations of tuberculin and three concentrations of either streptococcus or brucella control antigen in the presence of autologous plasma. A Hanks' solution control was included in each experiment. This is essentially a two-variable biologic system with dual controls for each variable. The migration in Hanks' solution and the cytotoxic index for each antigen concentration is shown in table 3. An analysis of these results is given in table 4.

It is evident that the higher concentrations of tuberculin, i.e., 1.0 and 0.5 mg. per ml., were toxic even for the cells of normal subjects. The concentration of 0.01 and 0.001 mg. of tuberculin per ml. was innocuous for cells of both tuberculin-negative and tuberculin-positive nontuberculous subjects. Only at 0.1 mg. per ml. concentration of tuberculin was there a significant difference between these two groups.

TABLE 3

SERIES I. CYTOTOXIC INDICES FOR AUTOLOGOUS CELL-PLASMA SYSTEMS OF TUBERCULIN-NEGATIVE (N), TUBERCULIN-POSITIVE (P), AND TUBERCULOUS (T) SUBJECTS IN TUBERCULIN AND CONTROL ANTIGENS

Subject	Date	Control Migration mm/16 hour	1.0	H37Rv Tuberculin mg/ml				Brucellergen® or Brucellin mg/ml			"Streptococcus 98" mg/ml		
				0.5	0.1	0.01	0.001	0.01	0.001	0.0004	0.2	0.1	0.04
N 1	4-24-52	1.9	0.58	0.90	1.00	1.00					0.73	0.84	0.97
2	8-4-52	2.7		0.91	0.95	0.98		1.01	0.91	1.07			
	9-22-52	2.4	0.73	0.93	0.97	1.07					0.73	0.97	0.96
	1-20-53	2.1	0.63	0.94	1.02	1.04	1.03				0.74	0.98	0.94
3	9-2-52	2.7	0.50	0.81	0.89	0.97		0.55	0.76	0.81			
	11-18-52	2.7	0.44	0.78	0.95	1.04		0.63	0.89	0.94			
	1-22-53	1.1		0.74	0.98	1.02	1.05				0.49	0.56	0.73
	3-16-53	1.9		1.04	1.05	1.02	0.97		0.95	1.07			
4	12-1-53	2.4	0.67	0.86	0.93	0.96	0.97				0.58	0.94	0.89
5	4-1-53	1.7	0.93	0.87	1.06	1.24		0.79	0.95	0.86			
	4-23-53	2.8	0.74	0.87	0.91	0.98					0.98	0.88	1.02
	5-13-53	3.0	0.71	1.00	0.97	0.99		0.60	0.97	0.95			
6	4-1-53	2.0	0.90	0.95	1.02	0.97		0.79	0.80	0.81			
	4-23-53	3.6	0.70	0.78	0.84	0.92					0.75	0.84	0.90
	5-13-53	3.1	0.49	0.74	0.94	0.97		0.83	0.99	1.01			
P 1	4-6-52	3.2		0.92	1.00						0.68	0.81	
	6-2-52	2.0	0.72	0.82	0.96	1.03		0.93	0.92	1.02			
	7-26-52	3.5	0.57	0.72	0.76	0.92		0.69	0.81	0.97			
	9-8-52	2.8	0.75	0.81	0.84	0.97						0.81	0.93
2	4-16-52	2.0		0.95	1.00	1.00					0.60	0.70	0.85
	5-14-52	2.1	0.43		0.95	1.00	1.00	1.03*	1.00	1.00			
3	4-6-52	2.4		0.62	0.96						0.33	0.58	
	4-16-52	2.7		0.63	0.89	0.89						0.63	0.62
	5-14-52	1.3	0.39	0.63	0.85	1.07	1.00	1.07*	1.00	1.00			
	11-3-52	2.5	0.43		0.84	0.93					0.62	1.02	0.93
1–	1-20-53	1.9	0.47	0.87	0.82	1.06	0.98				0.56	0.88	0.89
	4-13-53	1.6		0.46	0.71	0.97	0.80				0.68	0.85	0.86
4	4-24-52	1.7		0.53	0.65	0.93					0.50	0.70	0.87
5	5-5-52	2.3	0.91	1.00	1.00	0.96		0.82	0.92	0.96			
	9-29-52	2.6	0.66	0.76	0.83	0.98					0.42	0.39	0.61
6	5-23-52	2.2	0.61		0.85	0.95	0.96	0.77*	0.91	0.97			
	10-2-52	2.2	0.47	0.48	0.75	0.87		0.66	0.81	1.00			
	10-9-52	1.8	0.58	0.89	0.87	1.09		0.44	0.75	0.93			
7	6-2-52	2.1	0.39	0.82	0.91	0.95		0.91	1.03				
	2-24-53	1.9		0.91	0.86	0.87	0.82		1.04	1.12			
8	10-2-52	2.0	0.71	0.86	0.91	0.90		0.37	0.58	0.56			
	10-9-52	1.6	0.38	0.87	0.92	0.98		0.44	0.50	0.86			
9	4-16-52	3.6		0.89	0.92	1.00					0.72	0.83	0.94
	7-2-52	2.4	0.69	0.80	0.98						0.73		1.03
	7-9-52	1.8	0.38	0.85	0.74	0.92		0.28	0.78	0.94			
	1-22-53	1.0		0.70	0.83	1.00	1.01				0.10	0.20	0.21
	2-2-53	1.9	0.59	0.77	0.93	0.90	0.97	0.69	0.94	1.02			
	2-9-53	1.8	0.59	0.63	1.00	1.06	1.02	0.62	0.95	0.98			
	2-19-53	1.8		0.63	0.75	1.02	0.86	0.75	0.74	1.02			

TABLE 3—CONTINUED

Subject	Date	Control Migration mm/16 hour	1:0	H37Rv Tuberculin mg/ml				Brucellergen® or Brucellin mg/ml			"Streptococcus 98" mg/ml		
				0.5	0.1	0.01	0.001	0.01	0.001	0.0004	0.2	0.1	0.04
10	9-29-52	1.7	0.67	0.83	0.80	0.80					0.65	0.95	
	2-16-53	1.8		0.76	0.94	0.89	1.02				0.76	0.85	0.95
11	10-9-52	2.4	0.52	0.76	0.92	1.08		0.69	1.02	0.92			
	11-3-52	2.6	0.63	0.88	0.97	1.15					0.63	0.99	1.05
	3-5-53	2.6	0.67	0.94	1.06	1.02	1.07				0.82	0.92	0.94
12	3-5-53	1.8	0.47	0.79	0.92	0.96	0.94				0.73	1.05	0.96
	3-16-53	1.0		0.93	1.04	1.05	1.07	1.14	1.09	1.05			
13	11-3-52	1.9	0.54	0.64	0.86	0.91					0.79	1.00	1.08
	11-18-52	2.0	0.44	0.69	0.85	1.03		0.70	0.79	0.94			
14	10-28-52	2.0	0.49	0.68	0.91	1.08	1.01				0.68	0.96	0.94
	11-6-52	1.7	0.57	0.73	0.87	0.90	1.10	0.57	0.68	0.92			
15	11-6-52	2.0	0.32	0.72	0.95	1.06	1.09	0.52	0.61	1.05			
	11-18-52	2.0	0.55	0.79	0.91	0.94		0.59	0.68	0.92			
16	2-2-53	2.8	0.54	0.82	0.97	1.04	1.02	0.70	0.91	0.86			
17	2-9-53	1.9		0.71	0.81	0.95	1.07	0.74	0.95	0.90			
	2-16-53	1.8	0.48	0.64	0.72	1.23	1.05				0.76	0.85	0.95
18	11-6-52	1.5	0.80	1.00	0.83	1.08	1.13	0.58	0.61	0.99			
	1-22-53	1.6		0.84	0.72	0.87	1.00				0.45	0.60	0.81
	2-16-53	2.9	0.69	0.82	0.76	0.85	0.96				0.65	0.83	0.85
	3-12-53	2.4		0.82	0.89	1.01	1.03		1.05	1.02			
	3-30-53	2.2		0.67	0.86	0.89	1.07	0.94	1.04	1.01			
	4-23-53	3.0	0.60	0.74	0.87	0.97					0.91	0.91	0.92
	5-13-53	3.2	0.77	0.99	0.97	0.92		0.81	0.85	0.97			
19	4-1-53	1.4	0.85	1.13	1.03	1.05		0.94	0.94	0.98			
20	4-1-53	1.9	0.79	0.72	0.98	0.94		0.98	0.91				
21	4-23-52	2.5	0.86	0.94	0.95	1.03					0.77	1.03	0.95
T 1	4-6-52	3.0		0.50	0.60						0.66	0.76	
	4-16-52	1.1		0.50	0.50	0.73					0.73	0.73	1.00
	3-23-53	3.1		0.40	0.43	0.77	0.96				0.66	0.72	0.76
	4-13-53	2.4		0.59	0.59	0.89	1.00				0.92	0.88	0.87
2	4-16-52	3.7		0.57	0.80	0.75					0.62	0.92	0.84
3	4-24-52	1.9		0.69	0.74	0.89					0.84	1.00	1.00
	8-4-52	2.1		0.88	0.74	0.88		0.98	0.94	0.96			
4	5-5-52	1.9	0.63	0.84	0.84	0.84		0.79*	0.84	0.84			
5	5-5-52	2.5	0.48	0.60	0.60	0.56		0.84*	0.92	0.90			
	8-4-52	2.4		0.88	0.90	1.01		0.89*	0.93	0.97			
6	5-14-52	2.1	0.52		0.81	0.86	1.00	0.95*	0.93				
	5-23-52	2.4	0.53		0.93	0.98	1.05	0.88*	0.89				
7	5-23-52	3.0	0.76		1.04	1.02	0.98	0.96*	0.97				
	7-26-52	3.1	0.61		0.84	1.07		0.47	0.94	0.94			
	9-8-52	1.9	0.55	0.64	1.00	1.04						0.84	0.87
8	5-14-52	2.7	1.15		1.15	1.10	1.00	0.90*	1.05	1.10			
	5-23-52	2.4	0.72		0.93	0.98	1.04	0.97	1.03	1.01			
9	6-2-52	1.0	0.52	0.80	0.77	1.09		0.34	0.87	0.90			
10	7-2-52	2.3	0.48	0.67	0.80	1.04					0.74	1.09	0.95
	9-2-52	2.0	0.64	0.82	1.05	0.98		0.63	0.85	0.97			

TABLE 3—CONTINUED

Subject	Date	Control Migration mm/16 hour	1.0	H37Rv Tuberculin mg/ml				Brucellergen* or Brucellin mg/ml			"Streptococcus 98" mg/ml		
				0.5	0.1	0.01	0.001	0.01	0.001	0.0004	0.2	0.1	0.08
11	7-2-52	1.9	0.22	0.41	0.51	0.88					0.82		
	7-26-52	1.7	0.24	0.24	0.56	1.02		0.96	1.02	1.04			
	9-22-52	1.6	0.38	0.57	0.62	0.65					0.18	0.51	0.74
	3-23-53	1.7		0.53	0.58	0.97	1.08				0.96	0.86	0.91
	4-13-53	2.5		0.66	0.44	0.65	0.94				0.40	0.77	0.80
12	7-2-52	2.5	0.55	0.73	0.66						0.94		0.94
	3-25-53	1.9		0.60	0.41	0.68	0.68					0.75	0.91
13	7-9-52	2.2	0.39	0.52	0.73	1.00		0.45	0.68	0.84			
14	7-9-52	2.2	0.47	0.51	0.72	0.90		0.57	0.81	0.97			
	8-4-52	2.8		0.69	0.90	0.85		0.88	0.96	0.84			
15	9-2-52	1.3	0.51	0.61	0.81	0.91		0.80	0.90	0.90			
	9-22-52	1.0	0.39	0.64	0.88	1.03					0.68	0.94	0.92
16	9-8-52	1.7	0.19	0.25	0.35	0.44						0.92	0.97
	9-29-52	2.0	0.17	0.20	0.26	0.25					0.61		0.80
	11-6-52	2.2	0.37	0.39	0.45	0.40	0.63	0.39	0.66	0.82			
	3-25-53	1.4		0.25	0.36	0.25	0.68				0.56		0.72
	3-30-53	1.5		0.56	0.54	0.58	0.80	0.57	0.63	0.75			
	5-13-53	2.1		0.64	0.68	0.77	0.79	0.67	0.86	1.00			
17	10-2-52	1.7	0.77	0.87	0.84	0.76		0.90	0.87	0.95			
	10-9-52	1.0	0.83	0.62	0.85	1.00		1.17	0.88	0.92			
18	10-28-52	2.0	0.38	0.35	0.36	0.53	1.01				1.02	1.07	1.19
	11-6-52	1.8	0.25	0.28	0.37	0.37	0.71	0.42	0.70	0.83			
	2-24-53	2.3		0.27	0.31	0.28	0.58	0.84	0.87	0.84			
	4-15-53	2.0		0.49	0.44	0.48	0.52				0.98	0.98	1.11
	4-23-53	2.2		0.59	0.70	0.61	0.98				0.74	1.06	1.06
19	1-22-53	2.0		0.60	0.82	0.83	1.00				0.76	0.85	0.91
	2-2-53	2.0	0.48	0.71	0.94	1.03	0.96	0.43	0.97	0.94			
20	2-16-53	2.9	0.10	0.26	0.23	0.30	0.68				0.68	0.83	0.93
	2-24-53	2.4		0.20	0.19	0.25	0.34	0.91	0.89	0.90			
21	3-12-53	2.2		0.68	0.81	0.80	0.97	0.95	0.98	0.01			
	4-13-53	2.5		0.72	0.91	0.83	0.89				0.90	0.93	0.98

* These tests were made with brucellin. Unmarked tests in the brucella antigen section were made with Brucellergen*.

A comparison of results from tuberculin-negative subjects and tuberculous subjects shows that the cells of the latter were, as a group, significantly more sensitive to tuberculin in all concentrations studied. Ten of the 21 tuberculous subjects showed increased cellular sensitivity to 0.1 mg. of tuberculin per ml. as shown by a cytotoxic index of 0.77[12] or less in one or more tests. Eight of these 10

[12] Mean migration index normal cells in normal plasma (all normal cells in table 3) containing 0.1 mg. per ml.: 0.91. Twice standard deviation of the mean: 0.14. Values below 0.77 are significantly low.

Earlier in the text it was indicated that subjects N-3 and N-6 had some degree of cutaneous reactivity to tuberculin but were classified as "tuberculin-negative reactors" in conformity with arbitrary clinical criteria. When data on the cytotoxic index for 0.1 mg. of tuberculin per ml. are calculated omitting these individuals, a mean cytotoxic index of 0.98 is

TABLE 4

CRITICAL RATIOS AND PROBABILITY VALUES FOR THE TOXIC EFFECT OF TUBERCULIN AND CONTROL ANTIGENS ON LEUKOCYTES STUDIED IN AUTOLOGOUS PLASMA

Antigen	Concentration	N_1	N_2	N_3	S_1	S_2	S_3	$\bar{X}_1$	$\bar{X}_2$	$\bar{X}_3$	$\frac{\bar{X}_1 - \bar{X}_2}{S\Delta 1}$	P	$\frac{\bar{X}_1 - \bar{X}_3}{S\Delta 2}$	P
Tuberculin	1.000	12	39	29	14.74	14.74	22.22	66.8	58.9	49.2	1.62	0.11000	2.97	0.003700
	0.500	15	52	45	8.67	13.21	19.02	87.5	78.3	55.6	1.48	0.16000	3.45	0.000760
	0.100	15	55	51	5.72	9.59	24.00	96.5	88.4	67.2	4.15	0.00006	7.98	<0.000001
	0.010	15	52	49	7.13	8.36	21.04	101.1	97.9	77.1	0.78	0.44000	6.82	<0.000001
	0.001	4	25	25	3.57	7.98	19.19	100.5	100.2	85.1	0.13	0.90000	3.64	0.000480
Brucella	0.0100	7	28	27	14.75	20.95	22.24	74.3	72.8	76.0	0.22	0.83	−0.24	>0.99
	0.0010	8	30	27	7.12	8.32	4.22	90.3	86.0	88.3	1.12	0.28	0.62	0.54
	0.0004	8	28	24	9.62	15.80	10.67	94.0	96.0	92.3	−0.58	>0.99	0.75	0.46
"Streptococcus 98"	0.20	7	23	21	14.35	17.28	19.78	71.4	63.6	73.3	1.20	0.25	−0.27	>0.99
	0.10	7	24	20	13.03	20.30	13.43	85.9	80.6	87.1	0.82	0.42	−0.21	>0.99
	0.04	7	22	22	8.29	5.57	11.64	91.6	87.0	91.7	1.35	0.20	−0.03	>0.99

$\bar{X}$ = mean; N = number in the series; S = standard deviation.

Given above are the critical ratios (C.R.) for normal tuberculin-negative reactors (N_1, S_1, and $\bar{X}_1$) compared with both normal tuberculin-positive reactors (N_2, S_2, and $\bar{X}_2$) and tuberculous patients (N_3, S_3, and $\bar{X}_3$).

The critical ratio is found from the expression $\text{C.R.} = \frac{\bar{X}_1 - \bar{X}_2}{S\Delta}$.

The standard difference, $S\Delta$, is found from the expression $S\Delta = \sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2}}$.

Probability values are taken from standard tables. Note that significant specific tuberculin cytotoxicity occurred at a concentration of 0.5 mg. per ml. of cell suspension for tuberculin-positive normal subjects and throughout the concentrations tested for patients. Brucella and streptococcus antigens were not specifically more toxic for patients than for controls.

were sensitive to 0.01 mg. per ml., and 4 showed cellular hypersensitivity to 0.001 mg. per ml.

On theoretical grounds, it might have been expected that buffy coat tissue cultures from subjects with active tuberculosis all should have shown a uniform toxic-type response to tuberculin. The considerable degree of variability among patients was the most interesting observation in this series.

Analysis of the cellular response to streptococcus and brucella antigen of control subjects, nontuberculous tuberculin-positive reactors, and tuberculous patients showed no significant difference in sensitivity to these antigens (table 4).

Series II. Plasma Versus Cellular Factors in Tuberculin Cytotoxicity

The time involved in doing the kind of experiment used in *Series I* necessarily limited to two the number of major variables which could be manipulated at one time. In the experiments of *Series II* a fixed tuberculin concentration was used. This permitted an evaluation of the role played by plasma as well as by cells in tuberculin toxicity.

Plasma and washed cells were prepared by the same protocol as that described for *Series I* experiments in the preceding section of this study and were mixed in various combinations as described below. Only one tuberculin concentration (0.1 mg. per ml. final concentration) was used in this experimental series. The cells and the plasma of tuberculin-negative healthy subjects (normals) are designated respectively as NC and NP. The cells and plasma of tuberculin-positive nontuberculous subjects are designated as PC and PP. The cells and plasma of the tuberculous subjects are designated as TC and TP.

Series II experiments were done in two different groups. In the first group the cells of patients were studied in autologous plasma (TC/TP), in the plasma of other patients (TC/TP), and in the plasma of normal subjects (TC/NP). The cells of normal subjects were studied in autologous plasma (NC/NP), and in patient plasma (NC/TP). The cytotoxic index for these various combinations of cells in plasma are given for a group of five similar experiments in table 5. Significant differences in means for these experiments are given in table 7.

In the second group of *Series II* experiments, the cells and plasma of patients and of nontuberculous positive subjects were exchanged. The four combinations studied were TC/TP, TC/PP, PC/TP, and PC/PP. The cytotoxic indices for five representative experiments in this group are given in table 6. These data and those from a larger number of the same type of experiment, comprising in all 35 different patients (TC and TP) and tuberculin-positive comparisons (PC

obtained with 2 sigma equal to 0.09. With this norm, values below 0.89 would be significantly low among tuberculin-positive normal subjects and patients. Since the theoretical cytotoxic index should be unity, the latter method of calculation more accurately reflects the biologic phenomenon here under study. It is probable that subjects N-3 and N-6 had not experienced a tuberculous infection but had acquired a degree of sensitivity to tuberculin from exposure to saprophytic or other acid-fast bacilli which induced a cross sensitivity to tuberculins of various origins. It makes no great difference in the final interpretation of the data in this paper whether one or the other of these two mean normal values is used. With either, it is apparent that tuberculin allergy which can be measured *in vitro* is an inconstant finding in the presence of known tuberculous infections.

TABLE 5

SERIES II, GROUP 1. THE ROLE OF PLASMA AND OF CELLS IN TISSUE CULTURE TUBERCULIN CYTOTOXICITY

Comparisons of Normal Cells and Plasma with Patient Cells and Plasma

Experiment	Cells	Plasma			
		TP-12	TP-16	NP-7	
1	TC-12	0.40	0.48	0.55	
	TC-16	0.31	0.36	0.49	
	NC-7	0.56	0.34	0.86	
		TP-61	TP-63	TP-64	NP-3
2	TC-61	0.93			0.86
	TC-63		0.76		0.86
	TC-64			0.34	1.10
	NC-3	0.93	0.73	0.68	1.00
		TP-32	TP-36	TP-39	NP-1
3	TC-32	0.64			0.70
	TC-36		0.55		1.00
	TC-39			0.88	0.79
	NC-1	1.00	0.88	1.00	0.85
		TP-53	TP-55	NP-3	
4	TC-53	0.49		0.79	
	TC-55		0.50	0.51	
	NC-3	0.73	0.70	1.14	
		TP-49	TP-51	TP-52	NP-2
5	TC-49	0.97	0.91	0.86	0.94
	TC-51	0.97	0.86	1.03	1.06
	TC-52	0.84	0.87	0.72	0.86
	NC-2	0.89	0.94	0.62	1.04

and PP), have been analyzed for significant differences in the same manner used in Group 1 experiments of *Series II*. The values for significance are given in table 7.

The migration of normal cells in normal plasma was not inhibited to a significant degree by 0.1 mg. of tuberculin per ml. The mean cytotoxic index of these experiments was 0.98, which is essentially the same finding reported in *Series I*. Nine TC/TP combinations were studied in which the plasma was that of patients whose cells were inhibited to a significant extent (cytotoxic indices between 0.34 and 0.76) by 0.1 mg. of tuberculin per ml. in autologous plasma (table 5). In seven of these nine experiments, normal cells were also inhibited to a significant extent in the presence of tuberculin (cytotoxic indices between 0.34 and 0.73 in experiments 1, 2, 4, and 5 (table 5)).

The data in table 7 summarize these findings which are given as individual

TABLE 6

SERIES II, GROUP 2. THE ROLE OF PLASMA AND OF CELLS IN TISSUE CULTURE TUBERCULIN CYTOTOXICITY

Comparison of Nontuberculous Positive Cells and Plasma with Patient Cells and Plasma

Experiment	Cells	Plasma		
		TP-57	TP-58	PP-23
1	TC-57	0.90	0.90	0.91
	TC-58	0.75	0.79	0.72
	PC-23	0.95	0.95	0.90
		TP-65	TP-66	PP-1
2	TC-65	0.52	0.95	0.81
	TC-66	0.54	0.89	0.77
	PC-1	0.40	1.20	0.86
		TP-16	TP-12	PP-18
3	TC-16	0.54	0.25	0.86
	TC-12	0.70	0.43	0.95
	PC-18	0.31	*	0.86
		TP-31	TP-33	PP-22
4	TC-31	0.82	0.63	0.93
	TC-33	0.65	0.72	0.85
	PC-22	0.64	0.66	0.80
		TP-21	TP-1	PP-3
5	TC-21	0.91	0.18	0.91
	TC-1	0.85	0.59	0.79
	PC-3	0.92	0.60	0.71

* Cytotoxic index could not be calculated due to accidental breakage of saline control.

experiments in tables 5 and 6. Inspection of the P values for Group 1 experiments of *Series II* indicates that there is a significant difference between the toxicity of tuberculin for normal cells when they are suspended in tuberculous plasma instead of their own plasma (NC/NP vs. NC/TP; $P = 0.01$). This effect is clearly a property of the tuberculous plasma. When normal plasma is used to suspend both types of cells (NC/NP vs. TC/NP; $P = 0.06$), there is a borderline difference between cytotoxic indices suggesting that washed tuberculous cells possess some degree of sensitivity to tuberculin.

A considerable proportion of the lowered cytotoxic index is correlated with the presence of tuberculous plasma, however, as is seen in the comparison of normal cells with tuberculous cells, each suspended in tuberculous plasma. Tuberculous plasma significantly lowered both indices, resulting in a lack of migration differences between the two (NC/TP vs. TC/TP; $P = 0.50$).

When both cells and plasma are exchanged, the mean cytotoxic indices are

TABLE 7

ABILITY OF PLASMA AND OF CELLS IN TISSUE CULTURE TO BE RESPONSIBLE FOR TUBERCULIN TOXICITY AT A TUBERCULIN CONCENTRATION OF 0.1 MG. PER ML. OF CELL SUSPENSION

Group	Comparison	Mean Cytotoxic Indices Compared		Significant Difference
1	NC/NP vs NC/TP	0.976	0.779	+ (P = 0.01)
	NC/NP vs TC/TP	0.976	0.739	+ (P = 0.001)
	NC/NP vs TC/NP	0.976	0.789	− (P = 0.60)
	NC/TP vs TC/TP	0.779	0.739	− (P = 0.50)
	NC/TP vs TC/NP	0.779	0.789	− (P = 0.50)
	TC/TP vs TC/NP	0.739	0.789	− (P = 0.50)
2	PC/PP vs PC/TP	0.928	0.896	− (P = 0.50)
	PC/PP vs TC/TP	0.928	0.861	− (P = 0.06)
	PC/PP vs TC/PP	0.928	0.915	− (P = 0.50)
	PC/TP vs TC/TP	0.896	0.861	− (P = 0.50)
	PC/TP vs TC/PP	0.896	0.915	− (P = 0.50)
	TC/TP vs TC/PP	0.861	0.915	− (P = 0.50)

Comparison of cytotoxic indices for patient cells (TC), nontuberculous positive cells (PC) and normal cells (NC) with their respective plasmas (TP, PP, and NP). The mean cytotoxic indices were derived from data described in *Series II* experiments and given in tables 4, 5, and 6. Significant difference was calculated by means of critical ratios given in the legend for table 4. The interpretation of these results is given in detail in the text.

also significantly low and not significantly different (NC/TP vs. TC/NP; $P = 0.50$). This is evidence that tuberculous cells are sensitive to tuberculin. It could also be evidence that the cells were not thoroughly washed free of autologous plasma. Tuberculous cells suspended in tuberculous plasma showed a significantly low cytotoxic index which was not significantly different from the low cytotoxic index for tuberculous cells in normal plasma (TC/TP vs. TC/NP; $P = 0.50$). Again this is evidence that washed tuberculous cells may be sensitive to tuberculin.

The studies with nontuberculous tuberculin-positive subjects instead of tuberculin-negative subjects are given for *Series II*, Group 2, in table 7. The findings can be summarized briefly by saying that the plasma and cells of the tuberculin-positive subjects behaved toward tuberculin at this concentration in so similar a fashion to that of the plasma and cells of patients that significant group differences were not found. Review of individual experiments in this series (table 6) indicates that certain "positive" normal persons behaved toward tuberculin much as did the tuberculin-negative normal subjects. Other "positive" normals were similar to patients with active tuberculosis.

DISCUSSION

It is evident that the data for these two series of experiments do not show a uniform tuberculin toxicity *in vitro* for cells from either tuberculin-positive

healthy persons or even from patients with active tuberculosis. These findings are in contrast to the data given in tabular form by Rich and Lewis (5) who indicate that cells of animals sensitive to tuberculin were uniformly more sensitive to tuberculin in plasma of both allergic and normal animals than were cells of normal animals. The Rich-Lewis data furthermore indicate that cells of normal animals were equally insensitive to tuberculin in both normal and "allergic" plasma. Elsewhere in their paper, however, Rich and Lewis reported that in other experiments, for which data were not given, they observed unexplained variations both in the migration and in the survival of cells. Although their experiments failed to demonstrate that plasma of hypersensitive animals was capable of rendering normal cells sensitive to tuberculin, in some instances the combination of tuberculin and plasma of hypersensitive animals was a less favorable medium for normal cells than normal plasma and tuberculin. It is possible that there may have been instances in which a barely detectable amount of sensitizing plasma factor was actually present. Other workers have not studied the role of plasma with *in vitro* cellular hypersensitivity in the manner it has been approached by Rich and Lewis or by the present investigators.

Among the 21 tuberculous patients in the present study, there were 10 who had peripheral blood leukocytes during one or more studies which were more sensitive to 0.1 mg. of tuberculin per ml. than were the cells from normal control subjects (cytotoxic index < 0.77). These 10 tuberculous subjects come closest to the situation reported for qualitative tissue culture studies on experimental animals. Other workers who have recently re-examined *in vitro* tuberculin toxicity have found similar large quantities of tuberculin necessary for "specific" *in vivo* tuberculin effects (12). These amounts are a thousand fold the quantity of tuberculoprotein which will elicit a specific cutaneous reaction in the same host from which the donor cells are obtained.

The control antigens used, streptococci, brucellin, and Brucellergin®, did not show a greater toxic effect on the cells of the tuberculous subjects than on cells from normal subjects. It would have been advisable to test a group of persons with either brucellosis or acute streptococcal infections for their *in vitro* cell response to tuberculin, but such subjects were not available for study.

The present observations on the relative lack of a quantitative correlation between *in vivo* and *in vitro* tuberculin toxicity for peripheral blood leukocytes are similar to studies in which suspensions of peripheral blood leukocytes (3, 33, 36, 38), splenic pulp cells (33), or thoracic duct leukocytes (36) have been exposed to tuberculin. Other earlier workers also have found that only selected tuberculous subjects demonstrated *in vitro* tuberculin cytotoxicity (3, 46).

In previous tissue culture work with tuberculin allergy, it has been implied that some sort of a humoral factor present on cells or perhaps transmitted in an as yet nondetectable form, brings about tissue sensitivity. Once present, this sensitivity is presumed to persist through cell multiplication (5, 9).

The many demonstrations that tuberculin allergy can be transferred passively in animals with washed cellular exudates (26, 27, 28), lymph node cells (26), spleen cells (26), and washed peripheral blood leukocytes in man (29, 31) shed

doubt on the interpretation that tuberculin allergy, once acquired, is permanent. Numerous workers have noted that this type of passively transferred tuberculin allergy, in contrast to that associated with a tuberculous infection, is not lasting. Furthermore, the weight of evidence now indicates that cells of epithelial origin taken from the tuberculin-sensitive host are insensitive to tuberculin once they are removed from the humoral-cellular environment of the intact animal. On the other hand, cutaneous reactivity in the intact host probably depends upon the presence of lymphocytes in the skin. A recent study by Hagerman with fluorescent dye techniques (47) indicates that washed cells which passively transfer allergy can be traced directly into the epidermis.

At the present time it is presumed that tissue culture studies showing tuberculin cytotoxicity represent the effect of tuberculin on a select group of host cells which are present at the site of tuberculin reactions. Here they act to "trigger off" the complex train of humoral and cellular events which make up the local hypersensitivity reaction. Studies on the effect of adrenal steroids in the tuberculin reaction indicate that a considerable portion of the delayed-type reaction is secondary and not primary (48). This is most clearly demonstrated in the ear-window observations of Ebert (49) who recorded the reversal by cortisone of the marked vascular effects with diapedesis of plasma and leukocytes from the capillaries which are produced by tuberculin (50).

It is likely that a major part of the tuberculin reaction in the animal body is the result of an internal passive transfer of tuberculin allergy. When tissue sites do not contain appreciable numbers of cellular and humoral elements to bring about a significant initial reaction, little response occurs. This is the situation in epithelial tissue cultures. On the other hand, when there is a prior presence of cellular and humoral elements in tissues which are exposed to tuberculin, *in vitro* cytotoxic effects in tissue cultures should be observed, as they have been. It may be reasoned that, in the intact host, much less tuberculin is cytotoxic because additional specific cellular and plasma components are "passively transferred" into the reaction site, thus accounting, first, for the delay and, second, for the intensity of the tuberculin reaction.

Although the number of patients in the present study is small, it is tempting to correlate the degree of *in vitro* tuberculin sensitivity with some feature of the individual patient's illness. Available data indicate that there were many lacks of such a correlation. The age, duration, extent, temperature, erythrocyte sedimentation rate, amount of weight loss, subsequent course of the disease, presence of tubercle bacilli in the sputum, presence of cavities or of fibrosis were not factors. Neither was there a close relationship between the degree of cutaneous reaction to tuberculin and *in vitro* findings. The only suggestion of a parallel to be found from clinical evaluation of the patients was the presence of recent pneumonia-like exudative disease as judged by serial roentgenographic observations. The subjective nature of roentgenographic evaluation makes any such correlation hardly more than an impression.

The present investigation into the mechanism of delayed-type allergy clarifies somewhat the place of "cellular sensitivity" in the tuberculin reaction. It is

evident that *in vitro* techniques for studying the toxic effect of tuberculin on cells offer only a limited insight into the mechanism of delayed-type allergic phenomenon. Results obtained by these techniques do not support the hypothesis that all cells in the allergic host are sensitive to the toxic effect of tuberculin. They suggest instead that tuberculin allergy *in vitro*, as well as *in vivo*, is mediated either by specialized cells or by humoral factors, one or both of which must be present locally before appreciable tissue damage takes place.

SUMMARY

In this report a modified tissue culture technique employing peripheral blood leukocytes contained in capillary tubes has been used to study the tuberculin allergy of human tuberculosis by *in vitro* means. Results are compared and contrasted with other *in vitro* studies on tuberculin allergy in experimental animals.

It has been found that *in vitro* observations of many types do not support the widely held belief that all cells of the tuberculous host are tuberculin-sensitive. Rather, it is found that tuberculin sensitivity, both *in vitro* and *in vivo*, is mediated by cells derived from the reticulum system. Under some circumstances, *in vitro* sensitivity depends on these cells. Under other circumstances, factors present in the plasma mediate *in vitro* tuberculin sensitivity as well.

Various discrepancies exist between the degree of cutaneous tuberculin allergy and tissue culture allergy in a given host. It is suggested that tuberculin cytotoxicity observed *in vitro* is that portion only of the tuberculin reaction *in vivo* which is specific. It is this limited specific toxic effect, however, which triggers into action complex nonspecific focal inflammatory changes. These in turn mobilize both cells and humoral factors which further augment the local tuberculin reaction.

In this small series of patients with moderately to far advanced tuberculosis, the degree of toxicity of tuberculin for the leukocytes of these subjects did not correlate with the morbidity or the prognosis of their disease.

SUMARIO

El Análisis con Histocultivos de la Hipersensibilidad a la Tuberculina en el Hombre

En esta investigación, se utilizó una técnica modificada de cultivo de tejidos, que emplea leucocitos de la sangre periférica contenidos en tubos capilares, para estudiar *in vitro* la alergia a la tuberculina de la tuberculosis humana.

Descubrióse que las observaciones *in vitro* de muchos géneros no apoyan la creencia muy difundida de que todas las células del huésped tuberculoso son tuberculino-sensibles. Resulta más bien que la sensibilidad a la tuberculina, tanto *in vitro* como *in vivo*, es transmitida por células derivadas del sistema reticular. En algunas circunstancias, la sensibilidad *in vitro* depende de esas células. En otras circunstancias, factores presentes en el plasma transmiten igualmente *in vitro* la sensibilidad a la tuberculina.

Existen varias discrepancias entre la intensidad de la alergia cutánea a la tuberculina y la alergia de los cultivos de tejidos. Sugiérese que la citotoxicidad tuberculínica observada *in vitro* es únicamente la porción de la reacción tuberculínica *in vivo* que es específica. Sin embargo, es este limitado efecto tóxico específico el que desencadena complejas alteraciones inflamatorias focales anespecíficas. Estas a su vez movilizan tanto células como factores humorales que aumentan aun más la reacción local a la tuberculina.

En esta pequeña serie de enfermos que padecían de tuberculosis que variaba de moderada

a muy avanzada, el grado de toxicidad de la tuberculina para los linfocitos de dichos sujetos no se correlacionó con la morbosidad o con el pronóstico de la enfermedad de los mismos.

RESUME

Analyse de l'hypersensibilité à la tuberculine chez l'homme par la culture de tissus

Dans ce rapport une technique de culture des tissus modifiée, utilisant des leucocytes du sang périphérique contenus dans un tube capillaire, a été employée pour étudier *in vitro* l'allergie à la tuberculose dans la tuberculose humaine. Les résultats sont comparés et opposés à d'autres études, *in vitro*, sur l'allergie à la tuberculine chez l'animal en expérience.

On a découvert que les observations *in vitro*, très variées, ne confirmaient pas la croyance largement répandue que toutes les cellules de l'hôte tuberculeux sont sensibles à la tuberculine. Au contraire, il a été observé que ce sont les cellules dérivées du système réticulaire qui sont vectrices de l'allergie à la tuberculine à la fois in vitro et *in vivo*. Dans certaines circonstances, l'allergie *in vitro* dépend de ces cellules. Dans d'autres circonstances, des facteurs présents dans le plasma transmettent également, *in vitro*, l'hypersensibilité à la tuberculine.

Il existe diverses différences chez un hôte donné entre le degré de l'allergie cutanée à la tuberculine et l'allergie des tissus en culture. L'article suggère que la cytotoxicité observée *in vitro* est la seule partie de la réaction à la tuberculine qui soit spécifique *in vivo*. C'est toutefois cet effet toxique limitée qui déclanche les altérations inflammatoires focales complexes non spécifiques. Ces modifications, à leur tour, mobilisent à la fois des cellules et des facteurs humoraux qui augmentent encore la réaction locale à la tuberculine.

Dans cette petite série de malades dont le degré de l'affection tuberculeuse s'échelonnait entre modéré et très avancé, le degré de toxicité de la tuberculine pour les leucocytes de ces sujets ne correspondait pas à la morbidité ou au pronostic de l'affection.

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"OPEN HEALING" OF TUBERCULOUS CAVITIES[1]

Incidence and Pathology in 240 Resected Specimens

J. ROBERT THOMPSON

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INTRODUCTION

Prior to the use of present-day antimicrobial agents, it was most unusual to see tuberculous cavities which showed evidence of "open healing." This mode of cavity healing has been described in detail by many morbid anatomists but all of them are quite emphatic about the rarity of such a lesion. While some argue that a cavity is not healed as long as the cavum remains open, it must be stressed that the disappearance of the tuberculous elements and replacement by fibrous tissue does constitute healing of the disease process per se. Melzer (1) proposed that the pathologic criteria for "open healing" should consist of sharp demarcation of the cavity by fibrous tissue, absence of tubercle bacilli in the wall, and the disappearance of caseation or other tuberculous elements.

While it is commonly supposed by many that epithelization of the cavity lining is in part a manifestation of "open healing," Huebschmann (2) and others have pointed out that epithelization of an "open-healed" cavity is the exception rather than the rule. Pinner (3, 4) believed that epithelization was extremely rare and occurred only in very small cavities. On the other hand, partial epithelization of chronic cavities, as Auerbach and Green (5) point out, is seen quite frequently. One can usually demonstrate with little difficulty that this epithelium is a continuation of the epithelium of a communicating bronchus. It has also been pointed out that this type of cavity healing is usually limited to cases of long-standing tuberculosis.

Because of the increasing incidence of this peculiar type of healing in surgically resected pulmonary tissue, all of the resected specimens obtained in this hospital from 1948 to 1954 have been reviewed. The results of this analysis form the basis of the present report.

METHOD

The material studied consists of resected pulmonary tissue from 335 consecutive cases of pulmonary tuberculosis observed during a six-year period from 1948 to 1954 (table 1). At least four sections were taken from the wall of each cavity and each section was stained with hematoxylin and eosin, Masson's trichrome stain, and Ziehl-Neelsen stain for acid-fast bacilli. Those lesions which bore any resemblance to bronchiectatic cavities or emphysematous blebs or bullae were eliminated from the series.

[1] From the Division of Laboratories, Municipal Tuberculosis Sanitarium, Chicago, Illinois.

TABLE 1

PNEUMONECTOMIES, LOBECTOMIES, AND SEGMENTECTOMIES FOR THE PERIOD 1948 TO 1954

Number of cases of cavitary lesions		240 (71.6%)
Unhealed cavities	217 (90.4%)	
"Open healed" cavities	23 (9.6%)	
Number of cases of no cavitary lesions		95 (28.4%)
Total number of cases		335

TABLE 2

AGE DISTRIBUTION OF 145 SURGICAL CASES FOR A ONE-YEAR PERIOD (APRIL, 1953, TO APRIL, 1954)

	Age in Years							Total	Per Cent
	0-9	10-19	20-29	30-39	40-49	50-59	60-69		
Number of cases	4	24	45	38	27	6	1	145	—
Cavitary lesions (all types)	2	15	37	27	20	1	0	107	73.7
"Open healed" cavities	1	3	5	2	2	1	0	14	13.0

OBSERVATIONS

Twenty-three (9.6 per cent) of the 240 cases of cavitary disease in this series showed changes typifying "open healing." The greatest incidence for any one year was from April, 1953, to April, 1954, during which period there were 14 cases (13.0 per cent) as shown in table 2. The table also reveals that the incidence in each age group parallels the incidence of cavities of all types. These changes included an open cavum with a smooth glistening lining that might or might not show trabeculation. The wall was usually quite thin and appeared fibrous. The surrounding lung tissue usually showed only minor changes and relatively uninvolved bronchi invariably communicated with the cavity.

The majority, 16 patients, showed complete healing; however, minute ulcerations and/or granulations were seen grossly in the balance, 7 of the patients. The granulations were yellow-gray in color, slightly elevated, and averaged 2 mm. in diameter. The ulcerations were irregular in outline, very shallow, and up to 5 mm. in maximum dimension. These granulations and ulcerations involved only a very small proportion of the total cavity surface.

Microscopically, the completely healed cavities showed an underlying pattern which was common to all, a dense layer of fibrous tissue with collagenous fibers paralleling the surface lining. None of the cavities was lined by epithelium; however, in one or two instances there was extension of the epithelium of the communicating bronchus for a very short distance into the cavity proper. The fibrous walls showed varying degrees of hyalinization, a few scattered lymphocytes, few to many blood vessels, and rather sharp demarcation from the adjacent lung parenchyma. Occasionally, an atypical giant cell was seen a short distance beneath the cavity lining and some foci of calcified material were found deep in the cavity wall.

The "unhealed" areas in the cavity lining were found to vary considerably. The pale yellow-gray granulations which were seen grossly proved to be small tubercles situated on top of a heavy fibrous layer and composed of fibroblasts and fibrocytes, a few epithelioid cells, atypical giant cells, varying degrees of central caseation necrosis (in some instances showing calcification), and scattered lymphocytes. In those areas which were ulcerated grossly, the lining membrane was found to be made up of granulation tissue with some recognizable epithelioid cells and few to many atypical giants cells. These atypical giant cells frequently contained laminated, dark purple calcified masses comparable to Schaumann's bodies commonly seen in sarcoidosis. In some of the calcified masses in the depths of the cavity wall, one could still see remnants of these giant cells. None of the cavity walls in either group showed any appreciable degree of anthracotic pigmentation.

Sections taken in each case from different levels of the several blocks of tissue of these unhealed foci were stained with Ziehl-Neelsen stain and no acid-fast bacilli were demonstrated. It has been our experience in the past that bacilli could be demonstrated frequently in the lining of a chronic unhealed cavity if a comparable number of slides were examined.

DISCUSSION

With the increased incidence of "open healing" of tuberculous cavities, there naturally arises much controversy over whether or not these cavities are actually healed. As mentioned above, it has been commonly thought in the past that such cavities would be completely healed if they were lined by epithelium, but in the present series of cases none of the cavities showed any epithelial lining. The 7 cases which showed cavities containing a few small ulcerations and granulations were considered only partially healed, even though no tubercle bacilli were demonstrated by staining the tissue.

In a description of "open healing" of cavities, Jaffe (6) pointed out that an occasional small epithelioid tubercle or small caseous area was noted in the fibrous wall and tubercle bacilli were demonstrated in these lesions. He believed that the infection might only be silent for a while and flare up again. However, this description was given many years ago, long before the use of antimicrobial therapy.

Even though efforts to demonstrate acid-fast bacilli in the small granulations noted in the present study were unsuccessful, one cannot deny the possibility that organisms were still present which could play havoc in the future. Whether or not a longer period of drug therapy prior to surgical intervention would have produced further healing is speculative. Bacteriologic studies of the cavities proper were not carried out because of the desire to preserve the anatomic relationship by immediate fixation. In 4 of the 23 cases, however, material was aspirated from the bronchi after the surgical specimen was sent to the laboratory, and in every instance this material was negative on microscopy, culture, and guinea pig inoculation.

It has been pointed out by some writers that it is difficult to differentiate

these cavities showing "open healing" from bronchiectatic cavities or emphysematous lesions; however, this did not pose any real problem in the present review because of the following reasons: Almost all of the cavities were located in the apex of the lung and serial roentgenograms showed typical cavities. There was a complete absence of any of the elements of the bronchial wall within the wall of any of these cavities, and the bronchi and other portions of the specimen did not suggest any degree of bronchiectatic change other than that commonly associated with chronic tuberculosis. Likewise, the uninvolved lung parenchyma did not show any degree of emphysema and there was a paucity of anthracotic pigment in the walls of the "open-healed" cavities.

Without a doubt this unusual type of cavity healing is definitely related to present-day chemotherapy. It has been specifically related to the use of isoniazid by Johnson and Hewitt (7) who described the roentgenographic findings on twenty-two patients as being cystlike cavities. Four of their patients underwent surgery, and the pathology of the lesions was similar to that described here. In the present series of cases, 20 of the patients had received isoniazid along with dihydrostreptomycin or streptomycin and para-aminosalicylic acid (PAS), and 3 patients had received only dihydrostreptomycin-PAS or streptomycin-PAS (table 3).

The fact that none of the specimens resected prior to 1952 showed evidence of "open healing" substantiates the belief that chemotherapy is a predominant factor. Auerbach (8) was one of the first to describe in detail the effect of streptomycin on the healing process of a tuberculous cavity. He pointed out that the tuberculous cavity from an untreated patient usually has a lining consisting of necrotic material and degenerating inflammatory cells, but in "open healing" this innermost layer apparently sloughs away leaving only the dense fibrous wall. Whether or not the cavity proper is rendered sterile before the last trace of caseation necrosis has vanished is open to question. Certainly complete bacteriologic studies of these unusual cavities are indicated. The finding of patent communicating bronchi in these "open-healed" cavities suggests that elimination of the cavity contents and the necrotic lining membrane is an important factor in the rapid healing.

One is at loss to explain the peculiar cellular response seen in the sections from these cavities which were believed to be partially healed. These unusual changes included the presence of atypical giant cells with laminated calcified masses within them, the relatively few epithelioid cells, early calcification of the central portion of those tubercles showing caseation necrosis, and submerged small

TABLE 3

PREOPERATIVE CHEMOTHERAPY IN 23 CASES OF "OPEN HEALING"

	Duration of Treatment		
	More than 12 months	6-12 months	Less than 6 months
Streptomycin and PAS	10	5	2
Dihydrostreptomycin and PAS	2	3	1
Isoniazid and PAS	4	12	4

TABLE 4

RACE AND SEX OF 145 SURGICAL PATIENTS FOR A ONE YEAR PERIOD (APRIL, 1953, TO APRIL, 1954)

	White	Negro	Other	Total	Male	Female
All surgical cases	76 (52.4%)	66 (45.5%)	3 (2.1%)	145	55 (38.0%)	90 (62.0%)
Cavitary lesions (all types)	58 (54.2%)	48 (44.8%)	1 (1.0%)	107	41 (38.3%)	66 (61.7%)
"Open healing" cavities	4 (28.5%)	10 (71.5%)	0 (0.0%)	14	4 (28.5%)	10 (71.5%)

masses of calcium within the fibrous wall. In addition, many small blood vessels were noted. Denst (9) reported similar morphologic changes in resected specimens from patients treated with isoniazid in which there were a large number of atypical giant cells, a surprising amount of fibrillary fibroblastic, non-necrotic granulation tissue, and a few Schaumann bodies.

It has been suggested by some that race is a factor in the incidence of "open healing." This contention is supported in table 4, as 10 of the 14 patients during the one-year period were Negroes and only 4 were white. Of the total number (23 patients) during the four and a half-year period, 15 were Negro patients. As shown by the table, the surgical cases were almost equally divided between white and colored patients. There were a few more women than men and the majority of "open healing" cases were seen in surgical specimens from women (71.5 per cent).

There is also a possibility that the immunologic relationship between the invading organisms and the host was a factor. All of the cavities seen in 20 patients showed the same type of "open healing," whereas the remaining 3 patients showed unhealed cavities present in the same specimen with "open-healed" cavities.

SUMMARY

A review of the surgically resected pulmonary tissue from 335 patients between the years 1948 and 1954 disclosed that in 23 cases "open healing" of tuberculous cavities took place. As shown in table 1, this represents 9.6 per cent of all the cavitary lesions and, while this is a significant figure, one should not lose sight of the fact that the remaining 90.4 per cent still show the "garden variety" of chronic tuberculous cavity. Of the 23 patients, 20 were given isoniazid along with dihydrostreptomycin-PAS or streptomycin-PAS. The cavities could easily be differentiated from bronchiectatic or emphysematous lesions. The unusual cellular reaction is described in detail and the pathogenesis is discussed.

SUMARIO

"Cicatrización Abierta" de las Cavernas Tuberculosas: Incidencia e Histopatología en 20 Ejemplares Resecados

Un repaso del tejido pulmonar resecado quirúrgicamente a 335 enfermos entre los años 1948 y 1954 reveló que en 23 casos había tenido lugar "cicatrización abierta" de las cavernas

tuberculosas. Según muestra la Tabla 1, esto representa 9.6 por ciento de todas las lesiones cavitarias y, aunque esta cifra es importante, no debe perderse de vista el hecho de que el restante 90.4 por ciento de enfermos todavía muestra la forma "floreciente" de caverna tuberculosa crónica. De los 23 enfermos, 20 recibieron isoniacida en combinación con dihidroestreptomicina o estreptomicina y ácido para-aminosalicílico. Fué fácil diferenciar las cavernas de lesiones bronquiectáticas o enfisematosas. Se describe a fondo la extraña reacción celular y se discute la patogenia.

RESUME

Cavernes tuberculeuses épithélialisées: Incidence et histo-pathologie dans 240 pièces de résection

Une étude des tissus pulmonaires réséqués chez 335 patients, entre les années 1948 et 1954, a révélé que dans 23 cas l'épithélialisation des excavations tuberculeuses s'était produite. Comme le montre le tableau 1, ceci représente 9,6% de la totalité des lésions cavitaires et, bien que ce chiffre soit significatif, il ne faut pas perdre de vue que les autres 90,4% des cas présentent encore le type ordinaire de la caverne tuberculeuse chronique. Parmi ces 23 malades, 20 recurent l'isoniazide associée à la dihydrostreptomycine ou à la streptomycine et à l'acide para-aminosalicylique. Les cavernes pouvaient être aisément distinguées des bronchiectasies et des lésions d'emphysème. Cette réaction cellulaire inhabituelle est décrite en détail et sa pathogénie est commentée.

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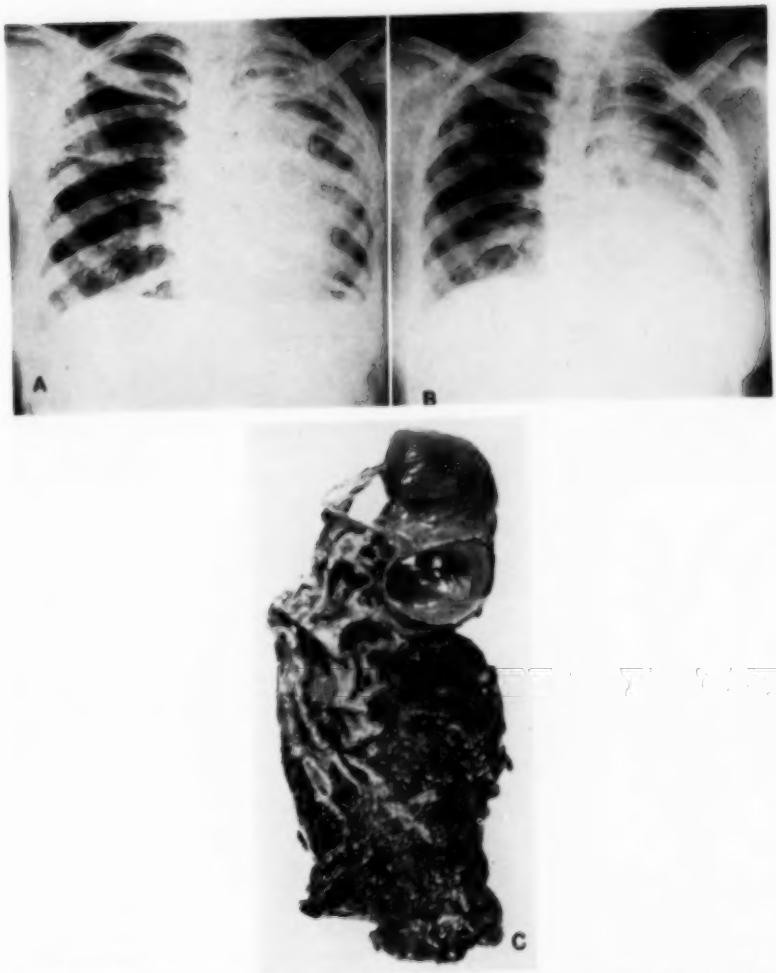

FIG. 1 (*A, B, C*). O. W., a 44-year-old white woman, was admitted to the Sanitarium on June 7, 1951; her illness dated back to 1949. She had been hospitalized at another institution from August, 1949, to July, 1950, during which time she received chemotherapy and pneumoperitoneum. Her sputum contained tubercle bacilli on admission. A chest roentgenogram taken on May 12, 1952 (figure 1*A*) reveals considerable involvement of the left chest with radiolucent areas in the left upper lung field and patchy infiltrations in the right lung. Streptomycin-PAS therapy was given from June, 1951, to December, 1951. Isoniazid was started on June 19, 1952; streptomycin-PAS therapy was restarted on December 6, 1952. A left pneumonectomy was performed on September 9, 1953. The patient was discharged on May 25, 1954. A roentgenogram taken on September 5, 1953 (figure 1*B*) shows some clearing on the right side, but little change is seen on the left. Figure 1*C* is a photograph of the left lung. There is a multiloculated cavity in the apex which has undergone "open healing."

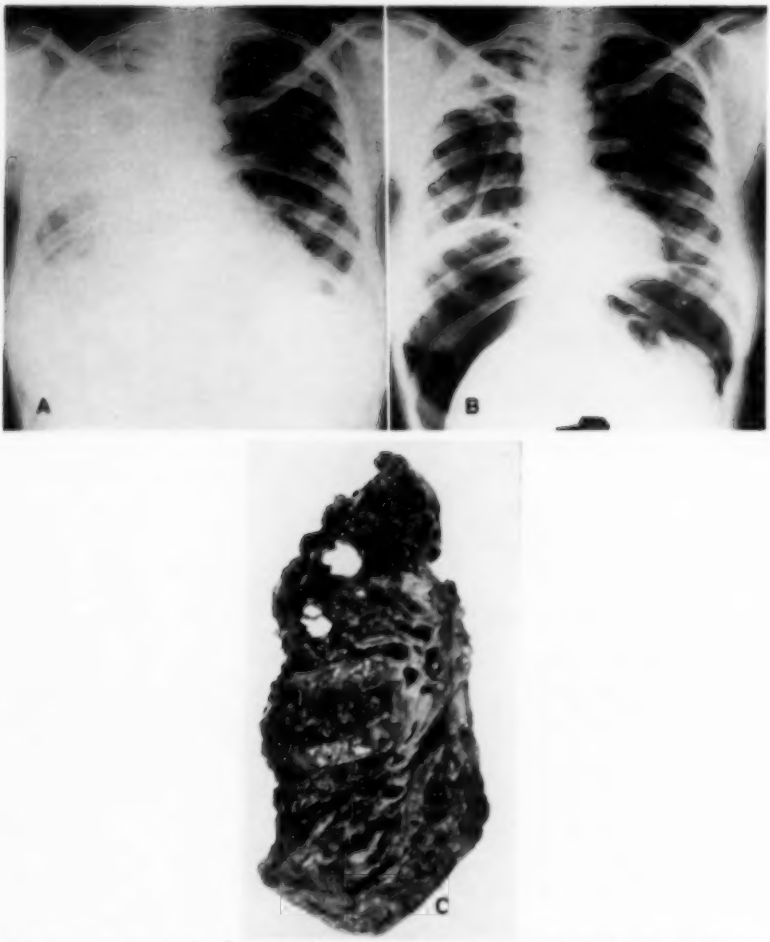

FIG. 2 (*A, B, C*). A. A., a 21-year-old Negro woman, was admitted to the Sanitarium on January 31, 1952, with a diagnosis of pulmonary tuberculosis and pregnancy. Sputum was positive for tubercle bacilli and the patient was very toxic. A roentgenogram taken on February 1, 1952 (figure 2*A*) revealed a homogeneous opacification obscuring the upper two-thirds of the right lung; a few ill-defined nodular densities were present in the lower half of the left lung field. Streptomycin-PAS therapy was started on February 3, 1952. The patient was delivered of a normal infant on April 28, 1952. Isoniazid therapy was begun on August 15, 1952, and pneumoperitoneum was instituted in November, 1952. On June 25, 1953, a roentgenogram (figure 2*B*) showed clearing of the exudative process in the right apex; there was a cavity present beneath the right second rib anteriorly. A right pneumonectomy was performed on August 18, 1953. This patient was discharged from the hospital with arrested tuberculosis on February 15, 1954. Figure 2*C* shows a multiloculated cavity with a glistening lining in the upper lobe of the right lung. There is a marked degree of bronchiectasis in the lower lobe with fibrosis of the surrounding parenchyma and obliteration of the interlobar fissures.

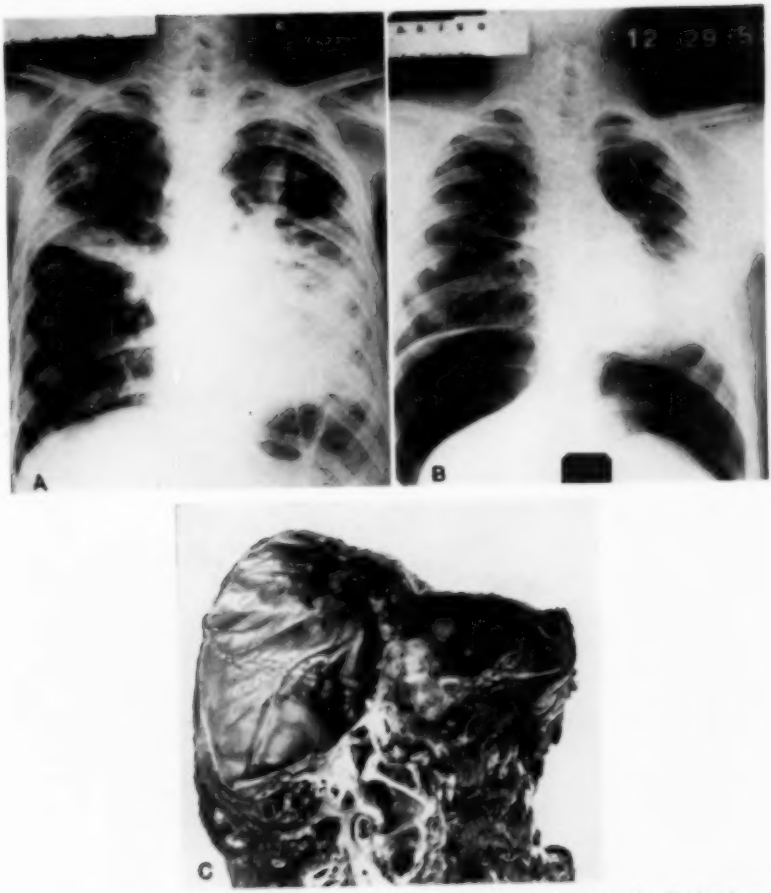

FIG. 3 (*A*, *B*, *C*). L. F., a 26-year-old Negro man, was admitted to the Sanitarium on February 27, 1953. Sputum was positive for tubercle bacilli, and the admission roentgenogram (figure 3*A*) showed infiltration, consolidation, and marked cavitation involving the entire left lung field and scattered infiltration in the right upper lung field. Streptomycin-PAS was given from February 28, 1953, to December 14, 1954, and isoniazid was given from January 13 to December 14, 1954. Pneumoperitoneum was maintained from August 11, 1953, to March 15, 1954, at which time a left pneumonectomy was performed. Sputum was negative for tubercle bacilli on microscopy and culture from April 20, 1953, to date of discharge, December 13, 1954. A roentgenogram taken on December 29, 1953 (figure 3*B*) shows considerable clearing of the nodular and exudative disease, but increase in size of the large cavity in the left upper lung field. Figure 3*C* is a gross photograph of the left lung showing a huge cavity in the apical portion with trabeculae coursing through it. The lining for the most part is smooth and glistening, but in one area the lining is dull appearing and has some small ulcerations. A large bronchus is seen to communicate with the cavity at the base.

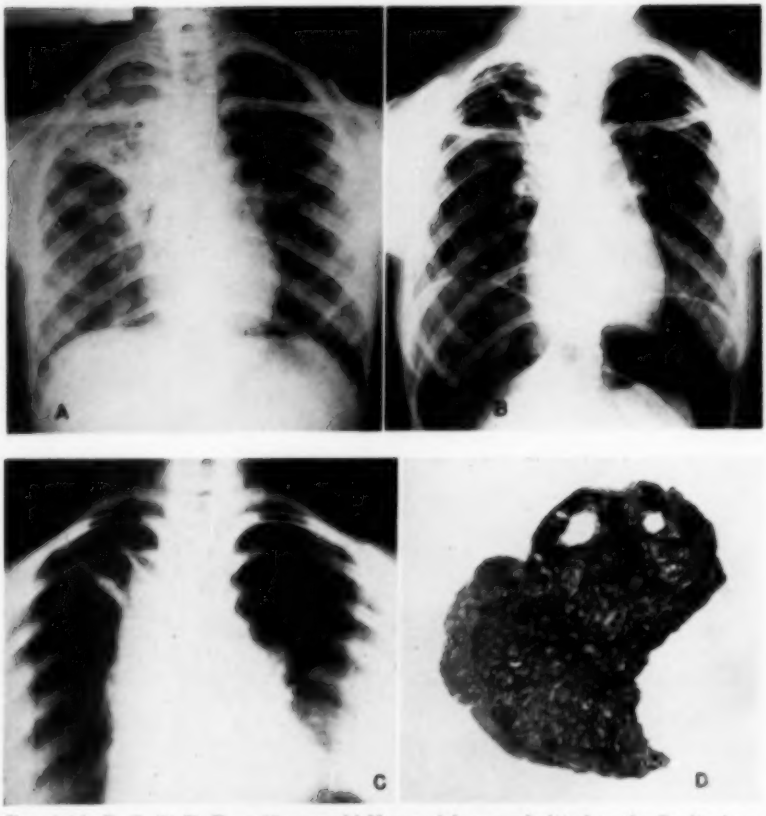

FIG. 4 (*A, B, C, D*) D. E., a 16-year-old Negro girl, was admitted to the Sanitarium on December 26, 1951. A roentgenogram taken at that time (figure 4*A*) shows a non-homogeneous opacification in the right upper lung field, with several radiolucent areas which were interpreted as cavities. There are a few soft mottled densities in the left mid-lung field. Sputum was positive for tubercle bacilli on microscopy at the time of admission and by culture until November, 1953. Dihydrostreptomycin-PAS therapy was given from December 28, 1951, to March 29, 1954. Figure 4*B* is a roentgenogram taken a few weeks prior to a right upper lobectomy (April 8, 1953). Tomograms taken at this time (figure 4*C*) show several large radiolucent areas in the right apex. Pneumoperitoneum had been instituted in July, 1952, and was abandoned just prior to surgery. The gross specimen photograph (figure 4*D*) shows several thin-walled cavities with smooth glabrous linings. Note the absence of pericavitary reaction. Careful dissection revealed one small fibrocaseous tubercle adjacent to one of the cavities.

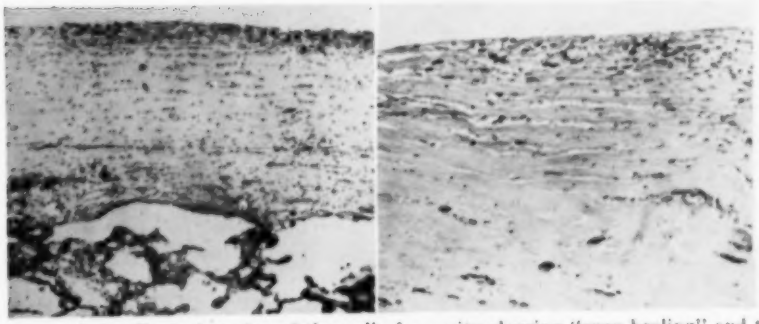

FIG. 5 (Left). Typical section of the wall of a cavity showing "open healing" and the adjacent lung parenchyma. Small blood vessels are noted and a few lymphocytes are scattered about. (× 100)

FIG. 6 (Right). A portion of a dense fibrous wall undergoing hyalinization. (× 150)

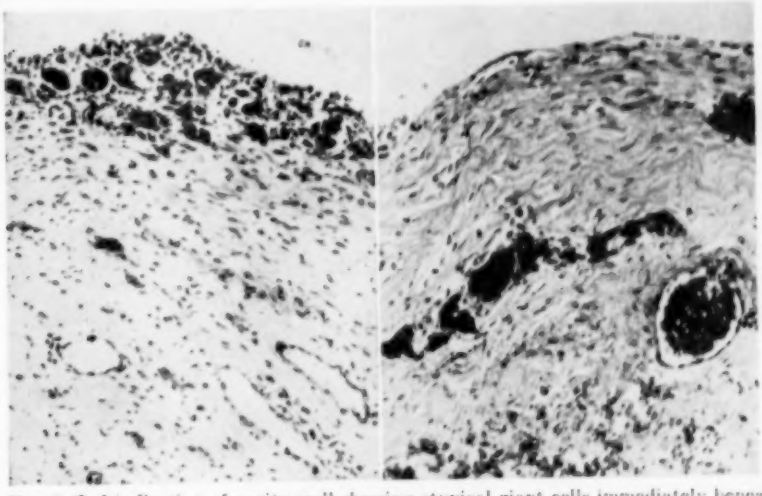

FIG. 7 (Left). Portion of cavity wall showing atypical giant cells immediately beneath the surface surrounded for the most part by fibrocytes and fibroblasts. (× 150)

FIG. 8 (Right). The wall of the cavity is composed of dense fibrous tissue in which collections of calcified material may be seen. (× 150)

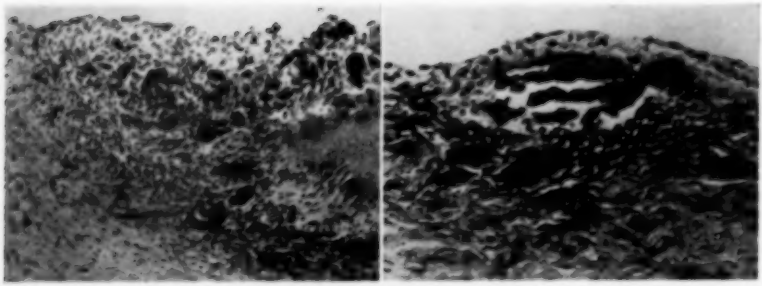

FIG. 9 (Left). Portion of a tubercle with a caseous center surrounded by some epithelioid cells, but chiefly fibrous tissue elements and atypical giant cells, some of which contain calcified material. There are several lymphocytes at the periphery of the tubercle and it is situated on top of a heavy fibrous wall. (× 150)

FIG. 10 (Right). A large collection of calcified material beneath the surface of the cavity with atypical giant cells showing calcification adjacent to it. (× 150)

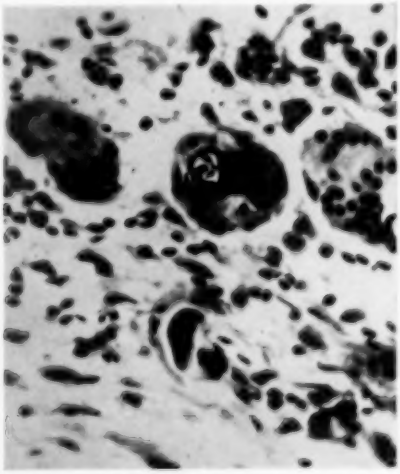

FIG. 11. Higher magnification of figure 6 to show atypical giant cells, one of which contains a laminated calcific mass within it. (× 400)

FACTORS INFLUENCING RELAPSE IN PULMONARY TUBERCULOSIS[1]

A Statistical Analysis of 1,259 Patients Followed from Eleven Months to Six Years After Discharge

TSUTOMU OYAMA[2]

(Received for publication March 25, 1955)

INTRODUCTION

The present study was undertaken to evaluate statistically the effects on relapse of various factors which might influence the outcome of pulmonary tuberculosis. The factors included were sex, extent of disease, age, condition on discharge, bacteriologic and roentgenographic data, regimens of chemotherapy, and types of other treatment. It is important to determine the various factors related to relapse in order to minimize the frequency of reactivations.

Numerous articles have been written about the outcome of pulmonary tuberculosis (15, 20, 27, 35, 61), but follow-up studies on modern treatment with antimicrobial therapy and resectional surgery have been infrequent. Furthermore, little can be found in the literature concerning the relative importance of factors related to relapse.

The value of any study of this type is proportional to the length of the follow-up observations. Nevertheless, yearly comparisons are difficult because of the rapidly changing trends in the treatment of pulmonary tuberculosis.

MATERIAL AND METHODS

The present study is concerned with a selected group of patients with pulmonary tuberculosis who were discharged from Glen Lake Sanatorium during the period from January 1, 1948, through December 31, 1953. Follow-up information included data up to November 30, 1954.

The analysis is based on the records of 2,571 discharged patients. Patients whose status fell within any one of the following categories were excluded from the original total:

1. Childhood type of tuberculosis
2. Pleurisy with effusion without demonstrable pulmonary lesions
3. Extrapulmonary tuberculosis
4. Short-term hospitalization (discharged within one month)
5. Deferred or nontuberculous diagnoses
6. Transfers
7. Irregularly discharged patient who returned to the sanatorium within one month
8. Death

These groups totaled 1,037 patients. Of the remaining 1,534 patients, follow-up data were available for 1,250 (82 per cent).

Relapse and progression of the pulmonary tuberculosis were treated synonymously. Relapse was designated as any unfavorable roentgenographic change consistent with tuberculous etiology, positive bacteriologic findings, or the development of a new extrapulmonary tuberculous focus. Discharges were classified in accordance with the 1950 edition of *Diagnostic Standards* (43).

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[1] From Glen Lake Sanatorium, Oak Terrace, Minnesota.

[2] Present address: University of Oregon School of Medicine Hospital, Portland, Oregon.

TABLE 1

FOLLOW-UP RESULTS ON 1,259 PATIENTS, JANUARY, 1948, THROUGH DECEMBER, 1953

Year of Discharge	Follow-Up Cases	Well (Nontuberculosis Death)	Active	Relapse (Tuberculosis Death)	R%*
1948	161	93 (13)	8	60 (12)	42.2
1949	162	102 (5)	7	53 (7)	37.0
1950	185	113 (6)	10	62 (11)	38.9
1951	215	149 (14)	8	58 (8)	30.7
1952	232	187 (9)	7	38 (3)	19.4
1953	304	256 (7)	25	23 (2)	15.8
Total	1,259	900 (54)†	65	294 (43)†	28.5

* Percentage of active plus relapse.

† = Deaths included in the data.

Follow-up letters were sent to each ex-patient and also to his physician or clinic. The following information was requested: the patient's present condition and specific symptoms, if any; the results of bacteriologic and roentgenographic examinations; and whether relapse had occurred and, if so, at what time. Follow-up letters on each ex-patient were compared so that the information would be as accurate as possible. Reports of visits of patients to the outpatient clinic were also utilized in this study.

The 1,259 patients were classified into two groups: those who were well at the time of survey and those whose disease relapsed after discharge from the hospital or who were found to have active tuberculosis. "Well" indicates that there had been no spread of disease and the patients were considered to have inactive tuberculosis. "Active" designates those patients whose lesions were not clinically and/or roentgenographically stable and who were regularly or intermittently shown to be discharging tubercle bacilli in the sputum.

The "*t*-test" for the significance of the differences between means and the "chi-square test" of independence were used in the statistical analysis. The *one per cent significant level* was used throughout. Thus, whenever a positive conclusion was reached, one might have at least 99 per cent confidence in it. The yearly relapse rates from 1948 through 1953 are shown in table 1.

RESULTS

Various Clinical Factors Possibly Related to Relapse

Sex: There were statistically significant differences in relapse rates in males and in females (table 2). In the youngest and oldest groups there were no great differences in relapse rates for males and females. However, the pulmonary tuberculosis relapsed approximately twice as often in men as in women in two age groups—thirty to forty-nine and fifty to sixty-nine. Other studies have reported that the relapse rate is higher in men than in women (19, 20) but did not emphasize the concomitant of age. Some writers have been unable to demonstrate a correlation between the relapse rate of pulmonary tuberculosis and the sex of the patient.

Extent of disease: It may be seen in table 3 that the extent of the tuberculous disease, roughly measured on the single roentgenogram obtained on admission to the hospital, is related to the subsequent reactivation of the disease. Relapse occurred twice as frequently in patients with far advanced pulmonary tuber-

TABLE 2

SIGNIFICANCE OF SEX AND AGE TO RELAPSE RATE (IN FOUR AGE GROUPS)

Age Group	Male			Female			Both Sexes		
	Cases	Relapse		Cases	Relapse		Cases	Relapse	
		Number	Per Cent		Number	Per Cent		Number	Per Cent
years									
All ages*	732	257	35.1	527	102	19.4	1,259	359	28.5
10–29†	148	32	21.6	220	41	18.6	368	73	19.8
30–49‡	300	110	36.6	224	41	18.2	524	151	28.8
50–69§	242	98	40.4	63	10	15.9	305	108	35.4
70+‖	42	17	40.5	20	10	50.0	62	27	43.5

* $\chi^2 = 37.07$; ndf = 1; $P < 0.001$—very highly significant.
† $\chi^2 = 0.46$; ndf = 1; $P \simeq 0.50$—not significant.
‡ $\chi^2 = 21.48$; ndf = 1; $P < 0.001$—very highly significant.
§ $\chi^2 = 13.25$; ndf = 1; $P \simeq 0.001$—highly significant.
‖ $\chi^2 = 0.50$; ndf = 1; $P \simeq 0.50$—not significant.

TABLE 3

EXTENT OF LESIONS IN RELATION TO RELAPSE

Extent of Lesions*	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
Minimal	137	82.6	29	17.4	166
Moderately advanced	462	73.7	165	26.3	627
Far advanced	301	64.6	165	35.4	466
Unilateral and Bilateral†					
Bilateral	545	65.4	288	34.6	833
Unilateral	355	83.3	71	16.7	426
Right‡	199	85.4	34	14.6	233
Left	156	80.8	37	19.2	193
Total	900	71.5	359	28.5	1,259

* $t = 4.9$; $P < 0.01$—significant
† $\chi^2 = 47.0$; ndf = 1; $P < 0.001$—very highly significant.
‡ Difference: $\chi^2 = 1.18$; ndf = 1; $P \simeq 0.30$—not significant.

culosis (35.4 per cent) as among those with minimal lesions (17.4 per cent). Similar observations have been reported by virtually all other writers with only a few exceptions (15, 33).

Unilateral and bilateral lesions: Relapse rates were significantly higher in patients with bilateral pulmonary lesions (34.6 per cent) than in patients with unilateral lesions (16.7 per cent). Differences between left and right pulmonary lesions among the unilateral cases were not remarkable (table 3). Douady and associates (15) reported that bilateral disease appeared to exert an unfavorable influence on the ultimate outcome, while Schwatt and Rest (54) believe that right-sided lesions are less serious than those in the left lung.

TABLE 4

AGE AND EXTENT OF LESIONS ON ADMISSION IN RELATION TO RELAPSE

Age of Patient	Minimal		Moderately Advanced		Far Advanced		All Groups			
	Well	Relapse	Well	Relapse	Well	Relapse	Well	Relapse	Total	R%*
years										
10–19	34	2	15	6	3	2	52	10	62	16.2
20–29	45	9	120	30	78	24	243	63	306	20.6
30–39	23	3	113	30	75	32	211	65	276	23.6
40–49	12	5	82	36	68	45	162	86	248	34.7
50–59	14	2	74	28	47	32	135	62	197	31.5
60–69	4	5	36	24	22	17	62	46	108	42.6
70+	5	3	23	11	8	13	35	27	62	43.5
Total	137	29	462	165	301	165	900	359	1,259	28.5
Mean	33.0	42.4	40.4	44.6	40.3	45.7	39.1	44.9	40.7	
t	3.200		2.860		4.010		6.17			
P	0.001		0.004		<0.001		<0.01			
Sig.†	HS		HS		VHS		HS			

* Relapse percentage

† Sig. = Significant; HS = Highly significant; VHS = Very highly significant.

Age: The extraordinary influence which the age of the patient exerts on relapse may be seen in table 4. Patients in the older age groups at the time of hospital admission had a greater tendency to have relapse of tuberculosis. Combining the factors of age and extent of lesions, it became evident that the number of moderately and far advanced cases did not increase with advancing age. Age was related to relapse rate in each classification.

It has long been suspected that the age of the patient affects the outcome in pulmonary tuberculosis. In reviewing the literature, three different opinions with respect to the age factor were found: first, that the younger the patients, the greater is the tendency to relapse (10, 39, 56); second, that there is no relationship between relapse of disease and age of the patient (15, 57); and, third, that older persons have higher mortality rates from pulmonary tuberculosis than younger persons (3).

Type of discharge: The circumstances under which the patient left the hospital had a definite relationship to the chance of subsequent reactivation of the tuberculosis. The relapse rate among patients who left the hospital against professional advice was high (42.1 per cent) and was approximately twice that of regularly discharged patients (20.7 per cent). The term *regular discharge* is used in the present study to designate patients who were judged to have received the maximum benefit from hospital care and whose condition was satisfactory on discharge from the hospital. This was not true for the *irregular discharge* group which included 38.5 per cent of the patients.

Condition on discharge: The condition of the patients on discharge from the hospital correlated well with the chance of relapse as shown in table 5. The re-

TABLE 5

CONDITION ON DISCHARGE IN RELATION TO RELAPSE

Condition on Discharge	Cases	Well		Relapse	
		Number	Per Cent	Number	Per Cent
Inactive	243	215	88.4	28	11.6
Arrested (IV)	457	371	81.1	86	18.9
Arrested (III)	70	42	60.0	28	40.0
Active, improved	314	196	62.4	118	37.6
Active, unimproved	175	76	43.4	99	56.6
Total	1,259	900	71.5	359	28.5

$\bar{X}_W = 2.51$; $\bar{X}_R = 3.56$; $t = 12.4$; $P \ll 0.01$—highly significant.

$\bar{X}_W$ and $\bar{X}_R$ denote the mean of the "well" and "relapse" groups, respectively; the symbols will be used in subsequent tables without explanation.

TABLE 6

PRESENCE OR ABSENCE OF CAVITY ON ADMISSION AND DISCHARGE IN RELATION TO RELAPSE

Roentgenographic Findings	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
On Admission*					
Noncavitary	356	74.3	123	25.7	479
Unilateral cavity	445	72.4	169	27.6	614
Bilateral cavities	99	59.6	67	40.4	166
Total	900	71.5	359	28.5	1,259
On Discharge†					
Noncavitary	844	77.4	246	22.6	1,090
Unilateral cavity	42	36.2	74	63.8	116
Bilateral cavities	14	26.4	39	73.6	53
Total	900	71.5	359	28.5	1,259

* $\bar{X}_W = 0.72$; $\bar{X}_R = 0.85$; $t = 3.15$; $P \simeq 0.01$—significant.

† $\bar{X}_W = 0.07$; $\bar{X}_R = 0.42$; $t = 11.97$; $P \ll 0.01$—highly significant.

lapse rate in the group discharged with active tuberculosis (56.6 per cent) was five times as high as the relapse rate in the group with inactive disease (11.6 per cent). Other follow-up studies have also demonstrated that the condition of the patient on discharge from the hospital does influence the outcome of pulmonary tuberculosis (24, 31, 52).

Presence of cavity: The relationship between subsequent relapse and the presence of cavitation on admission to, or discharge from, the hospital is definite (table 6). This is in accord with the widely accepted point of view which considers cavitation to be an unfavorable prognostic factor. There are some observers, however, who do not agree with this point of view (15, 33).

TABLE 7

BACTERIOLOGIC FINDINGS ON DISCHARGE IN RELATION TO RELAPSE

Bacteriologic Findings	Well		Relapse		Total
	Number	Per Cent	Number	Per cent	
Negative culture*	720	80.9	170	19.1	890
OG/OC (*a*)	182	90.1	20	9.9	202
OG/OC (*b*)	206	79.0	55	21.0	261
OG/OC (*c*)	332	77.7	95	22.3	427
Positive culture*	132	50.3	130	49.7	262
G/C (*a*)	89	66.5	45	33.5	134
G/C (*b*)	28	49.2	29	50.8	57
S	15	21.2	56	78.8	71
Negative on microscopy†	23	32.9	47	67.1	70
No sputum available‡	25	67.6	12	32.4	37
Total	900	71.5	359	28.5	1,259

$\bar{X}_W = 2.91$; $\bar{X}_R = 4.20$; $t = 12.9$; $P \ll 0.001$—very highly significant.

* Difference: $\chi^2 = 97.88$; ndf = 1; $P \ll 0.01$—highly significant.

OG/OC (*a*) More than 12 consecutive cultures for tubercle bacilli negative for at least one year.

OG/OC (*b*) More than 6 consecutive cultures for tubercle bacilli negative for six months.

OG/OC (*c*) Fewer than 6 consecutive cultures for tubercle bacilli negative for six months.

G/C (*a*) Occasional culture positive for tubercle bacilli for six months.

G/C (*b*) Culture for tubercle bacilli consecutively positive but specimens negative on microscopy for six months.

S Sputum positive for tubercle bacilli on microscopy.

† Negative on microscopy but no cultures obtained for six months.

‡ No sputum available for bacteriologic examination.

Bacteriologic findings on admission: Patients with sputum which revealed tubercle bacilli on microscopy at the time of hospital admission (36.2 per cent of the group) were twice as likely to have a subsequent relapse of their tuberculosis as those whose sputum and gastric contents were negative for tubercle bacilli by culture (19.9 per cent of the group).

Bacteriologic findings on discharge: The bacteriologic findings in the sputum or gastric contents appeared to be factors related to the rate of relapse. Patients from whose sputum or gastric contents tubercle bacilli could be cultured within six months of discharge were approximately twice as likely to experience a relapse as patients whose sputum or gastric washings were negative for tubercle bacilli by culture.

The bacteriologic status on discharge is tabulated in table 7. The lowest relapse rate (9.9 per cent) was found in the group designated OG/OC (*a*). This group consisted of those patients who had been noninfectious for at least one year preceding discharge, as demonstrated by at least twelve cultures of gastric contents or twenty-four- to seventy-two-hour specimens of sputum which were negative for tubercle bacilli.

The relapse rates in the OG/OC (*b*) group and the OG/OC (*c*) group were

similar. The first group included patients who had been noninfectious for six months prior to discharge, and the patients in the latter group had less than six monthly cultures negative for tubercle bacilli. Relapse occurred in approximately one-half of the G/C (*b*) group, all of whom had continued to discharge tubercle bacilli during the last six months of hospitalization. Moreover, relapse occurred in approximately 80 per cent of the "S" group, whose sputum consistently contained tubercle bacilli demonstrable by microscopy. These findings are in accord with the observations of others (1, 11).

Duration of disease: The duration of the pulmonary tuberculosis was measured from the onset of symptoms or from the date of diagnosis if symptoms were

TABLE 8

DURATION OF DISEASE IN RELATION TO RELAPSE

Duration of Disease	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
years					
0–1	52	61.1	33	38.9	85
1–2	202	73.7	72	26.3	274
2–3	151	72.2	58	27.8	209
3–4	85	69.7	37	30.3	122
4–5	67	74.4	23	25.6	90
5–10	171	71.5	68	28.5	239
10–15	75	75.7	24	24.3	99
15+	97	68.8	44	31.2	141
Total	900	71.5	359	28.5	1,259
Mean	5.92		5.92		

No difference.

TABLE 9

LENGTH OF HOSPITALIZATION IN RELATION TO RELAPSE

Length of Hospitalization	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
years					
0–½	127	66.5	64	33.5	191
½–1	158	66.1	81	33.9	239
1–2	377	75.0	125	25.0	502
2–3	149	73.7	53	26.3	202
3–4	51	71.8	20	28.2	71
4–5	19	70.4	8	29.6	27
5+	19	70.4	8	29.6	27
Total	900	71.5	359	28.5	1,259
Mean (months)	19.4		18.3		

$t = 1.36$; $P > 0.17$—not significant.

absent. The relapse rates were apparently unrelated to the duration of the disease (table 8). With one exception (38), these findings are in agreement with the reports of other writers (15, 39).

Length of hospitalization. It may be seen in table 9 that the duration of hospitalization bore no apparent relation to the occurrence of relapse. This corresponds to the experience in other studies (15, 39).

Regimens of Treatment in Relation to Relapse

Duration of bed rest: The data for 397 patients whose pulmonary tuberculosis was treated with bed rest alone during their hospitalization are presented in table 10. Duration of bed rest bore no demonstrable relation to relapse. The same conclusion stands out in each of the three subgroups for minimal, moderately advanced, and far advanced disease. Similar results have been found by others in patients with minimal pulmonary tuberculosis who were treated with "modified" bed rest (38, 39). Many other studies of bed rest noted by the present writer have been concerned with only minimal cases (4, 6, 38, 39, 47, 63, 64) except for one study in which it was concluded that strict bed rest was not superior to modified bed rest (14).

The term *bed rest*, as used in the present report, includes both "strict" bed rest and "modified" bed rest. "Strict" bed rest signifies that the patient spent twenty-four hours a day in bed, with transportation thereto or therefrom by litter or wheelchair. Patients on this regimen were allowed to sit up in bed, read, or listen to radio with permission, except during a daily rest period. "Modified" bed rest indicates that the patient was allowed various degrees of partial activity, ranging from one bathroom privilege to ambulation. In this group, at least eleven hours a day were spent in bed and meals were served in the dining room except for those patients with only bathroom privileges who had meals in

TABLE 10

LENGTH OF BED REST ALONE IN RELATION TO RELAPSE

Length of Bed Rest	Minimal		Moderately Advanced		Far Advanced		All Cases		
	Cases	Relapse	Cases	Relapse	Cases	Relapse	Cases	Relapse	Per Cent
months:									
0–3	20	5	29	11	25	11	74	27	36.5
4–6	19	4	57	10	24	9	100	23	23.0
7–12	50	13	79	42	32	16	161	71	44.1
13+	6	1	31	10	25	11	62	22	35.5
Total	95	23	196	73	106	47	397	143	36.1
t	0.06		1.59		0.64		1.29		
P	0.95		0.11		0.52		0.20		
Significant	NS*		NS		NS		NS		

* NS = Not significant.

TABLE 11

LENGTH OF STRICT BED REST COMBINED WITH OTHER TREATMENTS IN RELATION TO RELAPSE

Length of Strict Bed Rest	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
months					
0–3	169	67.8	80	32.2	249
4–6	162	67.5	78	32.5	240
7–12	309	72.7	116	27.3	425
13–24	180	77.5	52	22.5	232
25+	40	74.0	14	26.0	54
Total	860	71.7	340	28.3	1,200
Mean	9.9		8.8		

$t = 2.73$; $P \simeq 0.01$—significant.

bed. Patients were allowed to walk and have prescribed activities, but no outdoor exercise was permitted.

"Strict" bed rest combined with other treatments: The duration of "strict" bed rest combined with other forms of treatment was related significantly to re-

TABLE 12

TYPES OF COLLAPSE THERAPY, WITH OR WITHOUT CHEMOTHERAPY, IN RELATION TO RELAPSE

Type of Collapse	Minimal		Moderately Advanced		Far Advanced		Total	
	Cases	Relapse	Cases	Relapse	Cases	Relapse	Cases	Relapse
Collapse Alone*								
Thoracoplasty	2	0	68	23	36	12	106	35 (33.0)†
Pneumothorax	2	1	34	8	17	6	53	15 (28.3)
Pneumoperitoneum	3	1	10	1	10	4	23	6 (26.1)
Total	7	2	112	32	63	22	182	56 (30.8)
Collapse with Chemotheraphy‡								
Thoracoplasty	—	—	45	10	45	11	90	21 (23.3)
Pneumothorax	—	—	13	6	4	2	17	8 (47.1)
Pneumoperitoneum	—	—	18	4	21	9	39	13 (33.3)
Total	—	—	76	20	70	22	146	42 (28.8)

* $\chi^2 = 0.64$; ndf $= 2$; $P \doteq 0.75$—not significant.

† Percentage of relapse.

‡ $\chi^2 = 4.47$; ndf $= 2$; $P \simeq 0.10$—not significant.

lapse rates as shown in table 11. "Other forms of treatment" in this study refer to chemotherapy, collapse therapy, and excisional therapy.

There was no significant relationship between relapse rate and the duration of "bed rest" alone. However, when combined with other treatments, the length of strict bed rest was related to the relapse rate. Strict bed rest, therefore, still seems to play an important role in treating pulmonary tuberculosis as a specific form of therapy along with other treatments. In reviewing the literature, strict bed rest has long been considered the mainstay of treatment (4, 6, 50). Modified bed rest has been supported by others (8, 14, 38, 39), and some have even preferred combined rest and exercise (47).

Collapse therapy (thoracoplasty, pneumothorax, and pneumoperitoneum): The type of collapse therapy when used alone or when combined with chemotherapy demonstrated no significant relationship to the incidence of reactivation (table 12). These findings remained unchanged even when subdivided according to stage of disease.

The duration of chemotherapy when given with collapse treatment was usually less than three months. Streptomycin alone or streptomycin-PAS was given to most patients. The combination of collapse and short-term chemotherapy was prevalent from 1948 through 1951. Therefore, the observation period of these groups ranges from three to six years. Patients who were re-treated with lung re-

TABLE 13

REGIMEN OF CHEMOTHERAPY IN RELATION TO RELAPSE

Regimen	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
Streptomycin	116	65.5	61	34.5	177
PAS	11	61.1	7	38.9	18
Isoniazid	19	67.9	9	32.1	28
Streptomycin-PAS	322	84.5	59	15.5	381
Streptomycin-Isoniazid	48	88.9	6	11.1	54
Isoniazid-PAS	29	69.0	13	31.0	42
Streptomycin-Isoniazid-PAS	28	90.3	3	9.7	31
Total	573	78.4	158	21.6	731
Regrouped Regimen					
Streptomycin-Isoniazid-PAS or Streptomycin-Isoniazid	76	89.4	9	10.6	85
Streptomycin-PAS	322	84.5	59	15.5	381
Isoniazid-PAS or Isoniazid	48	68.6	22	31.4	70
Streptomycin or PAS	127	65.1	68	34.9	195
Total	573	78.3	158	21.7	731

Note: Original regimen: $\chi^2 = 38.94$; ndf = 6; $P \ll 0.01$—highly significant.
Regrouped regimen: $\chi^2 = 38.74$; ndf = 3; $P \ll 0.01$—highly significant.

section and those who received collapse procedure simultaneously combined with excisional surgery were included in the analysis of the excisional surgery group.

Chemotherapy: An analysis of the post-chemotherapy relapse rate and a breakdown of different chemotherapeutic regimens have been made to determine if any relationships to relapse could be demonstrated. Few studies of post-discharge observations on patients treated with chemotherapeutic agents have been published.

The several regimens of chemotherapy utilized in 731 patients, either alone or in combination with collapse or excisional therapy, are tabulated in table 13. Significant differences in relapse rates were demonstrated by the various regimens of chemotherapy. The efficacy of the different chemotherapeutic regimens, with or without other forms of treatment, was evaluated by measuring relapse rates.

The following list indicates the order of apparent effectiveness: streptomycin-isoniazid-PAS, streptomycin-isoniazid, streptomycin PAS, isoniazid-PAS, isoniazid alone, streptomycin alone, and PAS alone. As no statistically significant differences were noted between the groups which received streptomycin-isoniazid-PAS and streptomycin-isoniazid, isoniazid-PAS and isoniazid alone, the patients were re-grouped as follows: streptomycin-isoniazid-PAS or streptomycin-isoniazid, streptomycin-PAS, isoniazid-PAS or isoniazid alone, and streptomycin or PAS alone. Analysis of these re-grouped regimens yielded significant differences in terms of relapse rates.

The analysis suggested two points: the apparent superiority of streptomycin-isoniazid, with or without PAS, among the various multiple-drug regimens; and that streptomycin-PAS appeared superior to isoniazid-PAS. Definite conclusions cannot be drawn from the present material, however, because the number of patients was small and differences in the method of therapy existed in the different periods of observation.

TABLE 14

REGIMENS AND DURATION OF CHEMOTHERAPY WHEN USED ALONE* IN RELATION TO RELAPSE

Regimen of Chemotherapy†	Length of Chemotherapy (Months)‡							
	0-6		6-12		12+		Total	
	Cases	Relapse	Cases	Relapse	Cases	Relapse	Cases	Relapse
Streptomycin	47	18	1	0	6	2	54	20
PAS	1	0	0	0	0	0	1	0
Isoniazid	8	2	2	1	5	0	15	3
Streptomycin-PAS	48	16	32	9	40	6	120	31
Streptomycin-Isoniazid	8	2	11	1	6	0	25	3
Isoniazid-PAS	12	4	10	3	8	3	30	10
Total	124	42	56	14	65	11	245	67

* In contrast, the patients in table 13 include those who received surgical procedures as well as chemotherapy.

† $\chi^2 = 6.98$; ndf = 5; $P \geq 0.20$—not significant.

‡ $\bar{X}_W = 11.0$; $\bar{X}_R = 9.2$; $t = 2.49$; $P \geq 0.01$—significant.

TABLE 15

TYPE OF RESECTIONAL SURGERY IN RELATION TO RELAPSE

Type of Surgery	Minimal		Moderately Advanced		Far Advanced		Total		
	Cases	Relapse	Cases	Relapse	Cases	Relapse	Cases	Relapse	Per Cent
Wedge excision	13	1	29	2	7	0	49	3	6.1
Segmental resection	10	0	66	4	37	5	113	9	7.9
Lobectomy	2	0	34	5	35	5	71	10	14.0
Pneumonectomy	0	0	2	2	20	3	22	5	22.7
Total	25	1	131	13	99	13	255	27	10.5

$\chi^2 = 6.18$; ndf = 3; $P \simeq 0.10$—not significant.

Regimen of chemotherapy alone: The data for 245 patients treated with chemotherapy alone are shown in table 14. No significant differences were found with respect to particular drug regimens. Important differences were revealed, however, when the duration of chemotherapy was analyzed. Patients treated with chemotherapy alone for more than one year had a relapse rate of 18.5 per cent, while those in the group which received chemotherapy alone for less than six months had a relapse rate of 33.8 per cent.

Type of excisional surgery: As shown in table 15, there was no significant correlation between relapse rate and the type of excisional surgery. Almost every patient who had lung resection received chemotherapy before and after surgery. The over-all relapse rate was 10.5 per cent in this series of 255 patients who received chemotherapy and excisional surgery. This approximates the experience of others (21, 42).

Length of hospital stay after excisional therapy: Patients whose postoperative hospitalization after excisional surgery was less than six months had a relapse

TABLE 16

LENGTH OF STAY AFTER LUNG RESECTION IN RELATION TO RELAPSE

Length of Stay	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
months					
0–6	38	79.2	10	20.8	48
7–12	109	89.3	13	10.7	122
13–24	74	94.9	4	5.1	78
25+	7	100.0	0	0.0	7
Total	228	89.4	27	10.6	255
Mean	11.5		8.3		

$t = 2.97$; $P \simeq 0.01$—significant.

TABLE 17

REGIMEN OF TREATMENT IN RELATION TO RELAPSE

Regimen of Treatment	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
All Cases*					
Resection	228	89.4	27	10.6	255
Chemotherapy 12 months	54	83.0	11	17.0	65
Chemotherapy 6–12 months	42	75.0	14	25.0	56
Chemotherapy 0–6 months	82	66.1	42	33.9	124
Collapse with chemotherapy	104	71.2	42	28.8	146
Collapse alone	126	69.2	56	30.8	182
Bed rest alone	254	63.9	143	36.1	397
Total	890	72.6	335	27.4	1,225
Minimal Cases					
Resection	24		1		25
Chemotherapy 12 months	6		0		6
Chemotherapy 6–12 months	6		0		6
Chemotherapy 0–6 months	20		3		23
Collapse alone	5		2		7
Bed rest alone	72		23		95
Total	133		29		162

All cases: $\chi^2 = 58.49$; adf = 6; $P \ll 0.01$—highly significant.

Minimal cases: $\chi^2 = 9.38$; ndf = 5; $P \simeq 0.10$—not significant.

* Thirty-four patients who received no specific treatments were excluded from this analysis.

rate of 20.8 per cent. Relapse occurred approximately twice as often in this group as among patients whose postoperative hospital stay ranged from seven months to a year (10.7 per cent). These data are presented in table 16. The length of stay after lung resection correlated significantly with relapse rate. This finding emphasizes the importance of a rather prolonged period of hospitalization following surgery.

Type of treatment: The influence of the program of treatment upon the incidence of relapse after discharge has been studied. The results of specific therapeutic regimens were comparable with each other on a statistical basis. Various opinions have resulted from studies published previously; some found a relationship between type of treatment and relapse (19, 56), but at least one writer observed no clear-cut relationship between these variables (33). The prominent relationship between the various therapeutic regimens and the subsequent incidence of relapse in the 1,225 patients are illustrated in table 17 and figure 1.

Although no significant difference with respect to type of treatment was found

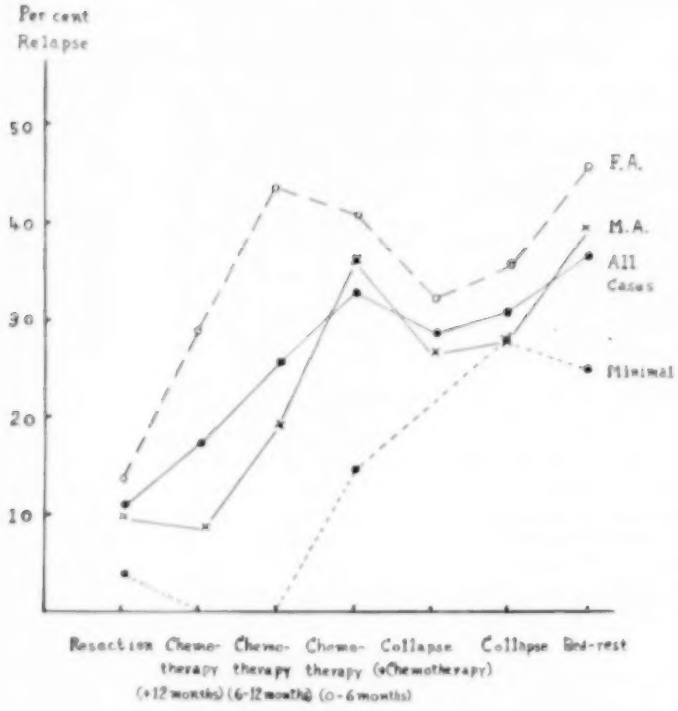

FIG. 1. Relationship between various therapeutic regimens and subsequent incidence of relapse in the 1,225 patients.

in cases of minimal pulmonary tuberculosis, the data for this group show trends or considerable numerical differences (table 17). The types of treatment in the groups with moderately advanced or far advanced tuberculosis influenced the relapse rate significantly (table 18). The long-term chemotherapeutic regimen (more than one year) alone seems to be slightly superior to lung resection for the minimal and moderately advanced groups; but for the far advanced group lung resection with chemotherapy was more effective than chemotherapy alone.

Collapse, with or without chemotherapy, was inferior to chemotherapy alone given for six months to one year for the minimal and moderately advanced groups. In the far advanced group, however, the former types of treatment were superior to chemotherapy alone. These results with respect to extent of disease suggest that, in general, chemotherapy alone is not sufficient for the far advanced group and that *some form of surgical treatment* usually seems necessary to prevent subsequent relapse

TABLE 18

REGIMEN OF TREATMENT IN RELATION TO RELAPSE

Regimen of Treatment	Well		Relapse		Total
	Number	Per Cent	Number	Per Cent	
Moderately Advanced Cases					
Resection	118	90.1	13	9.9	131
Chemotherapy 12 months	25	92.6	2	7.4	27
Chemotherapy 6–12 months	24	82.8	5	17.2	29
Chemotherapy 0–6 months	30	63.8	17	36.2	47
Collapse with chemotherapy	56	73.7	20	26.3	76
Collapse alone	80	71.4	32	28.6	112
Bed rest alone	123	62.8	73	37.2	196
Total	456	73.7	162	26.3	618
Far Advanced Cases					
Resection	86	86.9	13	13.1	99
Chemotherapy 12 months	23	71.9	9	28.1	32
Chemotherapy 6–12 months	12	57.1	9	42.9	21
Chemotherapy 0–6 months	32	59.3	22	40.7	54
Collapse with chemotherapy	48	68.6	22	31.4	70
Collapse alone	41	65.2	22	34.9	63
Bed rest alone	59	55.7	47	44.3	106
Total	301	67.6	144	32.4	445

Moderately advanced cases: $\chi^2 = 39.16$; ndf = 6; $P \ll 0.01$—highly significant.
Far advanced: $\chi^2 = 26.93$; ndf = 6; $P < 0.01$—significant.

DISCUSSION

The inclusion of relapse data for patients who received chemotherapy alone or with excisional therapy and the duration of the follow-up observations make the present report different from earlier studies. Great effort was made to analyze the material with the aid of appropriate statistical techniques.

The factors of relapse in pulmonary tuberculosis are so complicated that one factor may be analyzed alone without finding any apparent association with the rate of reactivation but, if combined with another factor, it may be found to have a significant correlation with the incidence of relapse. In the present study, this has been shown in the case of "strict" bed rest when associated with other forms of treatment and chemotherapy when used with other forms of therapy.

Analysis in the present study revealed that the post-treatment relapse rate for pulmonary tuberculosis was definitely higher in males than in females. If the age was also taken into account, however, it was found that there were no important differences in relapse rates for the two sexes in certain age groups, namely, ten to twenty-nine and in patients more than seventy years of age.

Patients in the older age groups had a greater propensity to relapse. This is in contrast to other studies which reported a favorable prognosis in older age groups (10, 39, 56).

Two possible explanations for this finding in the present study deserve comment. The older age groups had less adequate total treatment during the acute phases of tuberculosis and this was also probably true in the pre-chemotherapy and pre-resection era. Furthermore, their age would often make resectional surgery unfeasible. More attention should be paid to the older age group whose so-called "latent" tuberculosis has a great potentiality for progression.

On the present hospital service, streptomycin was used alone until 1950. At that time, streptomycin-PAS was used in a few patients, but the majority still received streptomycin alone (1 gm. daily) for less than three months. Long-term regimens (more than one year), consisting of streptomycin (1 gm. twice weekly) with PAS (12 gm. daily) were initiated in 1952. At about the same time, the use of isoniazid (300 mg. daily) was instituted either alone or along with streptomycin.

The patients, who were on regimens of streptomycin alone or with PAS for three months or less, were observed from three to six years. The patients who received isoniazid alone, isoniazid-streptomycin, or streptomycin-PAS for prolonged periods were observed from eleven months to two years. Why apparently significant differences were found among regimens of chemotherapy combined with other treatments but not among the regimens when used alone cannot yet be answered.

The type of treatment appeared to influence significantly the incidence of reactivation. It was evident throughout this study that prolonged chemotherapy for one year or more was remarkably effective, as was lung resection combined with chemotherapy. Resectional surgery plus chemotherapy demonstrated superiority over chemotherapy alone in patients with far advanced tuberculosis but this was not found true in patients with moderately advanced tuberculosis.

SUMMARY

Two thousand five hundred seventy-one patients were discharged from Glen Lake Sanatorium from 1948 through 1953. Of this total, 1,534 patients were found to have an uncomplicated adult type of pulmonary tuberculosis which could be adequately evaluated. Sufficient follow-up reports were obtained in 1,259 patients and these patients were observed for periods ranging from eleven months to six years. The cumulative incidence of reactivation during the period of observation following discharge was 28.5 per cent.

Significant relationships were demonstrated between incidence of relapse and the following factors: sex, extent of disease, unilateral and bilateral lesions, age, circumstances surrounding hospital discharge, condition on discharge, bacteriologic findings on admission, bacteriologic findings on discharge, presence or absence of cavity on admission and discharge, duration of "strict" bed rest combined with other treatments, regimens of chemotherapy combined with other treatments, length of chemotherapy, and type of treatment.

There were no significant correlations between the incidence of relapse and the following: (*1*) right or left pulmonary lesions among unilateral cases, (*2*) duration of disease, (*3*) length of hospitalization, (*4*) duration of "bed rest" alone, and (*5*) the particular regimens of chemotherapy when used alone.

SUMARIO

Factores que Afectan la Recidivación en la Tuberculosis Pulmonar—Análisis Estadístico de 1,259 Enfermos Seguidos de Once Meses a Seis Años Después del Alta

Dos mil quinientos y setenta y un enfermos fueron dados de alta del Sanatorio Glen Lake de 1948 a 1953 inclusive. De este total, en 1,534 se descubrió que tenían una forma adulta de tuberculosis pulmonar sin complicaciones, que podía ser valuada adecuadamente. En 1,259 se obtuvieron suficientes informes subsiguientes, manteniéndose a los enfermos en observación durante períodos que variaron de once meses a seis años. La incidencia acumulativa de la reactivación durante el período de observación consecutivo al alta fué de 28.5 por ciento.

Se observaron relaciones significativas entre la incidencia de recidivas y los siguientes factores: sexo, extensión de la enfermedad, lesiones uni- y bilaterales, edad, clase de alta, estado de salud al dar el alta, hallazgos bacteriológicos al ingreso, hallazgos bacteriológicos al dar el alta, presencia o falta de cavernas al ingreso y al alta, duración del "absoluto descanso en cama", combinado con otros tratamientos, duración de la quimioterapia y forma de tratamiento.

No hubo correlaciones significativas entre la incidencia de recidivas y y los siguientes factores, (*1*) lesiones del pulmón izquierdo o derecho en los casos unilaterales, (*2*) duración de la enfermedad, (*3*) duración de la hospitalización, (*4*) duración del "descanso en cama" solo y (*5*) los regímenes de quimioterapia cuando se usaron por sí solos.

RESUME

Facteurs influençant les rechutes dans la tuberculose pulmonaire-Analyse statistique concernant 1.259 patients suivis de onze mois à six ans après la sortie du sanatorium

Deux mille cinq cent soixante et onze patients sont sortis du sanatorium de Glen Lake de 1948 à 1953 inclus. Parmi ce nombre, 1.534 malades présentaient une tuberculose pulmonaire de type adulte non compliqué qui pouvait être évaluée correctement. Des rapports adéquats relatifs à la post-cure ont été obtenus pour 1.259 patients; ceux-ci étant suivis pendant des périodes allant de onze mois à six ans. L'incidence cumulative de la réactivation pendant la période d'observation post-sanatoriale s'élevait à 28,5%.

Une concordance significative a été démontrée entre l'incidence des rechutes et les facteurs suivants: sexe, étendue des lésions, lésions unilatérales et bilatérales, age, modalités de la sortie, état au moment de la sortie du sanatorium, conditions bactériologiques à l'admission et à la sortie, présence ou absence de cavernes à l'admission et à la sortie, durée de"l'alitement strict" combiné aux autres traitements, durée de la chimiothérapie et type de traitement.

Il n'y avait pas de corrélation significative entre l'incidence des rechutes et les conditions suivantes: 1) lésions pulmonaires droites ou gauches dans les formes unilatérales, 2) durée de l'affection, 3) durée de l'hospitalisation, 4) durée de l'alitement seul, 5) modalités de la chimiothérapie, quand elle était utilisée exclusivement.

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INVESTIGATION OF IRREGULAR DISCHARGE OF TUBERCULOUS PATIENTS[1]

A Special Ward Procedure for Reducing Against-Medical-Advice Discharges

THOMAS H. LORENZ,[2] JOSEPH M. GREEN,[2] WILLIAM C. LEWIS, MILDRED STONE, GEORGE CALDEN, AND JOHN R. THURSTON

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INTRODUCTION

A number of pressing needs in relation to the irregular discharge problem were emphasized in a previous publication from this hospital (1). In the first place, it is essential to understand accurately the nature and causation of irregular discharge. Second, it is necessary to develop reliable means of detecting and predicting those patients who have the strongest potential for irregular discharge. Lastly, it is imperative to find *practicable* measures for prevention of irregular discharge.

Some observations relative to the first consideration recently have been presented (2, 3) and at least one device, which is proving of value in the early detection of potential irregular discharge patients, also has been reported (4).

The present communication is concerned with one approach to the third need, i.e., a practicable technique for dissuading or preventing tuberculous patients from leaving the hospital against medical advice. The present report is based on twelve months' experience with a special discharge ward procedure designed for reducing discharges against medical advice.

MATERIALS AND METHODS

General

The Veterans Administration Hospital, Madison, Wisconsin, is a 486-bed institution for the treatment of military veterans with tuberculosis. The vast majority of the hospital population are males with the pulmonary form of tuberculosis. The occasional female patient and the few males with nonpulmonary tuberculosis included in the total hospital census have been excluded from this study. There are three categories of irregular discharge: patients who leave the hospital against medical advice (AMA), patients who fail to return from a professionally sanctioned several-day absence from the hospital (AWOL), and patients who are discharged from the hospital because they consistently break hospital regulations—a so-called disciplinary discharge (DD). In some hospitals, usually those having a liberal policy on the question of short absences from the hospital, the majority of irregular discharges are of the absent-without-leave variety. Most of the irregular

[1] From the Psychosomatic Department of the Medical and Tuberculosis Service, Veterans Administration Hospital, Madison, Wisconsin.

[2] Deceased.

[3] Fellow, Menninger School of Psychiatry, temporarily assigned to Madison Veterans Administration Hospital. Present address: Veterans Administration Hospital, Topeka, Kansas.

discharges from the Madison Veterans Administration Hospital, however, have been of the against-medical-advice type. The procedure herein reported was designed to cope only with discharges against medical advice; it was not expected to affect directly the other types of irregular discharge.

Rationale

Weekly conferences, devoted to discussions of various aspects of the irregular discharge problem, have been held for several years at this hospital (3). It was observed that patients frequently demanded their clothes and obtained their "walking papers" in a setting of intense anger, frustration, or defiance. Such irregular discharges occurred as a result of an impulsive decision based on a temper tantrum, or some other transient emotional upset, and were not the result of a well thought out plan. As these were mentally competent patients, there seemed to be no alternative to that of acceding to their demands. Through the well-intentioned efforts of an able staff, working with dispatch and efficiency, these patients often found themselves "cleared" and outside the hospital within thirty minutes after they had requested their clothes.

A striking number of these patients soon regretted their precipitous behavior and wished to re-enter the hospital. In view of these "changes of heart," it occurred to the staff that, if obstacles could be thrown in the path of these rapid and efficient discharges and the patients held in the hospital long enough for deterrent efforts to be made, a number of them might reconsider their impulsive decision and decide not to leave the hospital. Given an opportunity to ventilate their feelings to a sympathetic or impartial listener, some patients might see their problems differently and decide to stay. Still others, who had problems outside the hospital which they had not previously discussed with any of the hospital staff, might become convinced that solutions were possible through the help of social service or other hospital facilities. Thus, they might be persuaded that their departure was neither necessary nor wise. Removing the patient from the emotionally charged situation on his own ward to a *new* ward might allow him to remain in the hospital without "losing face."

Previously, efforts had been made on the wards to persuade this type of patient to stay in the hospital. In the presence of his fellow patients, however, and with the suspicion that he was being "high pressured," attempts to "reason" with the patient usually were futile.

From these considerations, the special discharge ward procedure was devised.

Discharge Ward Procedure

A three-bed room was set aside as the special discharge ward. All patients demanding discharge against medical advice were sent there for processing. A staff physician, who coordinated the activities of all staff members concerned, was designated as the special ward doctor. She talked with patients about their medical status, the necessity for continued hospitalization, and their reasons for wanting to leave. In addition, she ordered various laboratory tests and medical procedures (sometimes optional ones) which were presented to the patient as

"necessary" before he could leave. A psychiatrist or psychologist from the Psychosomatic Department saw the patient and attempted to help him better understand how and why his proposed act would be against his best interests. A social worker usually visited the patient and offered help in finding a solution to problems outside the hospital while the patient remained in the hospital. Other staff members, who might have established a particularly good relationship with the patient or who were especially interested in his problem, were called upon to talk with him. Included among these staff members were the original ward doctor, the surgeon, the chaplain, members of the administrative or nursing staff, and, in some cases, fellow patients of the Patient's Council who had reached the ambulatory stage. A record was kept on the patient's chart in which each individual who saw the patient noted his impressions, his suggestions for effective ways of helping the patient to remain, and other significant observations.

The patient himself was advised that his roentgenograms and the state of his disease should be reviewed with him for his own welfare. Also, any unfinished laboratory tests should be completed for his discharge summary, so that, if he were to be rehospitalized, this information would be available to his new doctor. It was emphasized that he should know what medications were necessary for him and how to obtain them in order to continue some kind of therapy program outside the hospital. He should be instructed about the precautions necessary to protect the health of his family, his friends, and the general public. Likewise, he should be made aware of public health laws, public sentiment toward tuberculosis, and difficulties that he might have with various authorities. Finally, if and when it was agreed that the patient could not be persuaded to stay, he was "cleared." He received his clothes and money, and left.

It was intended that this procedure resemble (to the patient) the Medical Discharge Board at which various staff members confer with the patient to review his hospital course, his present medical status, and his plans for the future after he leaves the hospital. Thus, the special ward procedure was presented as a sort of "emergency board" to prepare the patient for discharge. After this presentation, the patient might decide to stay. Yet, even if he did leave against medical advice, a useful purpose had been served. He had been made aware of the dangers to himself and his community which would be imposed by his leaving the hospital before his tuberculosis had been arrested.

It was recognized that this procedure would be useless if the ward physicians did not understand the reasons for it and did not cooperate fully in its administration. The medical staff, therefore, was presented with the plan in order to solicit its cooperation. The methods and goals of this special discharge procedure were thoroughly explained and discussed. It was left to the discretion of the doctor to decide at what point the patient should be transferred to the special ward. He would be better able to distinguish those threats which were shallow from those which were serious. Rare instances were anticipated in which a patient would be either extremely adamant about leaving or panicky. In such a case, the doctor might judge it unwise to delay his departure and therefore would arrange for immediate clearance through the special ward. Similarly, the nursing staff

and ward personnel were carefully oriented in the role they would play in this plan. After this staff orientation, the hospital administration issued an official memorandum directing that all patients wishing to leave the hospital against medical advice *must* be transferred to the special ward before being discharged.

This special ward procedure has been conducted essentially as described above for more than a year. The present report of the first six months of its operation has been delayed six months in order to evaluate the follow-up results. It was considered important to know whether the patients who were "retrieved" by the special ward procedure remained in the hospital to complete their treatment. Also, an attempt was made to trace those patients who left against medical advice. This was done by examining the correspondence of the Social Service Department and the records of the hospital registrar. Finally, it was considered pertinent to determine whether the over-all irregular discharge rates of the hospital changed during this period of observation and to speculate on what part the special ward procedure played in any change which occurred.

RESULTS

The special discharge ward was opened on November 9, 1953. In the following six months there were twenty-six admissions to this ward of 24 patients, all of whom sought discharge against medical advice. Two-thirds of these patients were dissuaded from departing, i.e., they were "retrieved." Eight patients succeeded in leaving against medical advice.[4] During the twelve-month period after inauguration of this special discharge procedure, the hospital's rate of discharge against medical advice decreased from 36 to 15 per cent of discharges, and the total irregular discharge rate fell from 52 to 34 per cent.

Because of the possibility that certain characteristics might identify the 24 special ward patients as a group, their age, race, marital status, service connection, extent of disease, previous history of irregular discharge, and length of their

[4] Ten patients were discharged against medical advice during this six-month period who have *not* been included in these statistics. Of the 10, there were 3 instances in which the procedure was only a formality, i.e., the patients went to the ward, received their clothes, and left. The medical staff decided that these patients should not be encouraged to stay. One person, who had been "retrieved" once, was so disruptive to hospital routine that the only alternative to leaving against medical advice was a disciplinary discharge. The second patient was also a behavior problem whose relatives had arranged for his admission to a hospital which was not a Veterans Administration hospital. The third patient, who had almost completed his hospital treatment, was so restless and anxious about remaining in the hospital that his physician unofficially sanctioned his leaving. Thus, these 3 cases were regarded as "technical" discharges against medical advice, i.e., the staff decided they should go but could not allow them a regular discharge. During this time there were also 3 patients who received discharges against medical advice after being admitted for *emergency* treatment only. Finally, 4 patients received discharges against medical advice directly from their wards. Two of these patients previously had been "retrieved" on the special ward, but subsequently were not returned there because it was the intention of the ward doctors or administrative staff to be rid of these patients who were disrupting their wards. In the other 2 cases, there was simply misunderstanding of the procedure. The remainder of the discharges against medical advice, all of which are reported, were instances in which the patient wished to leave and the staff opposed this wish.

TABLE 1

COMPARISON OF 24 SPECIAL WARD PATIENTS WITH 100 IRREGULAR DISCHARGE PATIENTS AND 100 MAXIMUM-HOSPITAL-BENEFIT DISCHARGE PATIENTS

	Special Ward Patients	Irregular Discharge Patients	Maximum-Hospital Benefit-Discharge Patients
Number	24	100	100
Age (years)			
Mean	42	40	40
Range	26–61	21–73	21–65
Color (per cent)			
White	79	79	84
Negro	17	17	13
Other non-white	4	4	3
Marital status (per cent)			
Single	25	29	31
Married	33	56	56
Divorced	33	12	8
Widowed	9	3	5
Service connection (per cent)			
Service connected	42	32	34
Not service connected	58	64	66
Unjudicated	0	4	0
Extent of tuberculosis (per cent)			
Far advanced	67	45	21
Moderately advanced	25	37	44
Minimal	8	16	32
Not pulmonary	0	2	3
Previous irregular discharge (per cent)			
No record	33	54	79
One	33	26	14
Multiple	33	20	7
Length of hospitalization (days)			
Mean	180	148	260
Range	36–390	1–360	12–480

hospital stay before attempting discharge against medical advice were tabulated. These data have been compared with similar data from a previous study in which 100 patients who received the regular so-called maximum-hospital-benefit discharge were contrasted with 100 patients who received irregular discharge (2). As may be seen in table 1, the present series of 24 patients tends to resemble the previous group of irregular discharge patients.

On separating these 24 patients into those who were discharged from the special ward and those who were "retrieved" to return to various hospital wards, it is apparent that there are no major differences between the two subgroups (table 2).

The time each patient spent on the special ward and the number of people who saw him were recorded routinely. The average time spent on the ward was approximately thirty-two hours for the group who left and twenty-four hours for the group who were "retrieved." The range varied from one hour to eight days

TABLE 2

COMPARISON OF SPECIAL WARD PATIENTS WHO WERE DISCHARGED AGAINST MEDICAL ADVICE AND THOSE WHO WERE "RETRIEVED"

	Discharged Group	"Retrieved" Group
Number	8	16
Age (years)		
Mean	43	42
Range	33–59	26–61
Race		
White	8	11
Negro	0	4
Other non-white	0	1
Marital status		
Single	2	4
Married	2	5
Divorced	4	5
Widowed	0	2
Service connection		
Service connected	3	7
Not service connected	5	9
Extent of tuberculosis		
Far advanced	5	11
Moderately advanced	3	3
Minimal	0	2
Previous irregular discharge		
No record	2	6
One	3	5
Multiple	3	5
Length of Hospitalization (days)		
Mean	229	156
Range	120–390	36–360

and one hour to seven days, respectively. The average number of visits by different staff members was 2.4 to the group who left and 2.9 to the group who stayed. Twenty-one of the patients were seen by the physician in charge of the special ward, 17 were seen by one or more members of the Psychosomatic Department, 13 were seen by the social worker and 6 were seen by various other staff members. Several were also visited by fellow patients.

The direct results of the special ward procedure are reported in the limited sense of its goal and usefulness, i.e., as a means of decreasing against-medical-advice discharges by keeping the patient in the hospital during a period of crisis when he otherwise would have left. If, through this procedure, the patient reconsiders and returns to a hospital ward, the procedure is regarded as having been successful. As noted above, of twenty-six attempts by 24 patients to leave the hospital against medical advice, there were eighteen occasions when the patient was "retrieved" and eight instances in which the patient was discharged from the special ward.

TABLE 3

HOSPITAL DISCHARGES FOR YEAR PRECEDING AND YEAR FOLLOWING INTRODUCTION OF SPECIAL DISCHARGE WARD PROCEDURE

Type of Discharge	Before (Number of Patients)	After (Number of Patients)
Maximum hospital benefit	140	239
Irregular	151	121
Against medical advice	104	53
Absent without leave	27	51
Disciplinary	20	17
Rate of Discharge	**Per Cent**	**Per Cent**
Irregular	52	34
Against medical advice	36	15
Absent without leave	9	14
Disciplinary	7	5

Follow-up Observations

Follow-up of the eventual disposition of the 16 patients who were "retrieved" revealed that 8 patients later left the hospital irregularly (3 against medical advice, 4 absent without leave, and 1 disciplinary discharge) and the other 8 did *not* (2 maximum hospital benefits, 4 transfers, one postoperative death, and one remains in the hospital to date).

Among the 8 patients who were "retrieved" but later left irregularly, 4 were discharged within two weeks of their admission to the special ward. The other 4, however, were delayed an average of fifteen weeks.[5] Nine of the 16 "retrieved" patients returned to the *same* ward from which they had been transferred after demanding a discharge. Eventually, 5 of these patients left by irregular discharge. Of the 6 patients "retrieved" and transferred to a *different* ward, 2 later received an irregular discharge. The sixteenth patient, who was admitted to the special ward on three occasions, twice returned to the ward from which he had come and once went to a different ward. This patient subsequently left the hospital by disciplinary discharge.

Of the 24 original patients, therefore, 8 left against medical advice immediately, 8 were delayed but eventually left by some type of irregular discharge, and 8 did *not* leave by irregular discharge.

On follow-up of the 8 patients who left against medical advice from the special ward, it was found that 2 later returned to this hospital and one was admitted to another Veterans Administration hospital. The location and condition of the other 5 is unknown. Of the 8 patients who were "retrieved," but later left the hospital by irregular discharge, 4 subsequently were readmitted to this hospital and 4 could not be located.

[5] Although it is not possible to prove, it would seem reasonable to believe that fifteen weeks of additional treatment had a favorable effect on the course of the disease of these patients.

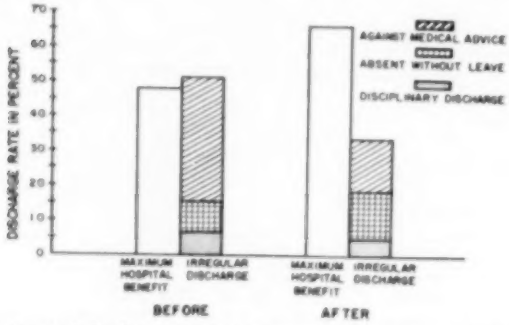

FIG. 1. Comparison of discharge rates for the year preceding and the year following introduction of special discharge ward procedure.

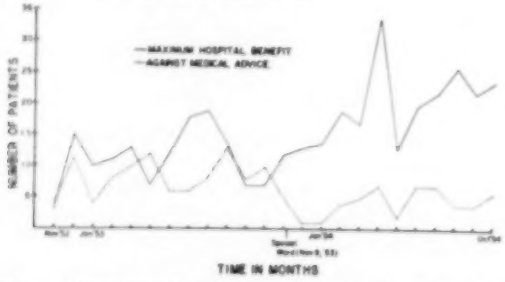

FIG. 2. Comparison of maximum-hospital-benefit and against-medical-advice discharges for the year preceding and the year following introduction of special discharge ward procedure.

Indirect Results of Procedure

During the year concurrent with the operation of this special discharge procedure, the rate of discharge against medical advice of this hospital decreased significantly. It may be seen in table 3 that, for the year preceding the opening of the special ward, the rate was 36 per cent of discharges whereas it has been only 15 per cent for the year following. The over-all irregular discharge rate[6] decreased in roughly the same proportion during this period of time; from 52 to 34 per cent. While the absent-without-leave and disciplinary discharge rates changed slightly, these alterations were not statistically significant (figure 1).

The number of maximum-hospital-benefit discharges and against-medical-advice discharges per month for the year preceding and the year following the introduction of the special discharge ward are plotted in figure 2. It is apparent

[6] The discharge rates quoted in this report are based only on maximum-hospital-benefit and irregular discharges. In the opinion of the writers, comparison of these two groups gives the most accurate picture of the issue under consideration. Transfers, deaths, observation and examination, not eligible for hospitalization, emergency treatment completed, administrative discharges, and patients not found to have tuberculosis were excluded. If all of the above were included, the irregular discharge rates would be lower, but the changes would be in the same proportion.

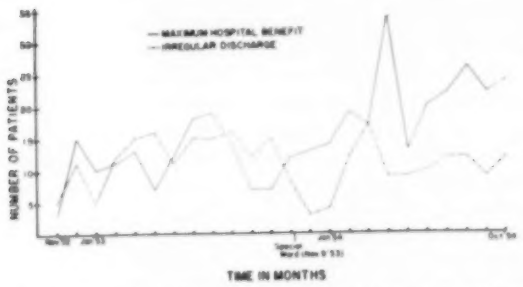

FIG. 3. Comparison of maximum-hospital-benefit and irregular discharges for the year preceding and the year following introduction of special discharge ward procedure.

that there was an abrupt decrease in discharges against medical advice immediately after the special ward was put into operation. Subsequently, the monthly rate of discharge against medical advice increased and then reached a plateau at approximately one half the level for the preceding year. The number of maximum-hospital-benefit discharges and the *total* number of irregular discharges per month are presented in figure 3.

DISCUSSION

During the six-month period of this study, two-thirds of the patients who sought against-medical-advice discharge were dissuaded through the use of a special discharge procedure. This result is encouraging but even more so is the finding that there was a concurrent decrease (from 36 to 15 per cent) in the rate of discharges against medical advice from the hospital. "Retrieving" 16 patients from the special ward, however, does not account entirely for this marked reduction in rate of discharge against medical advice. (They represent merely 4 per cent of discharges, not 21 per cent as would be required to explain the total decrease.) How, then, can this significant decrease in the rate of discharge against medical advice be explained? It is believed that the special discharge ward has a *suppressing* effect on attempts at discharge against medical advice before they occur and exerts this effect upon both patients and hospital staff.

Patients generally dislike going to the special discharge ward. They know that staff members will visit them on this ward and attempt to persuade them to stay. Many of them do not relish the thought of having to justify their intentions of leaving to the staff personnel, especially when they may realize, themselves, that their contemplated actions are unjustifiable. Rather than "run the gauntlet," these patients prefer to "sweat it out" on their wards, and the emotional crisis passes. Support for this is afforded by the fact that there were only 24 patients admitted to the special ward during the period of study. According to the previous rate of discharge against medical advice of this hospital (10 per month), *sixty* admissions to the ward would have been expected during this six-month period.

In addition, the presence of the special ward makes the entire hospital staff—particularly the ward physicians—more aware of the problem of discharges

against medical advice and better motivated to find constructive solutions for the difficulties and conflicts which prompt patients to leave the hospital in this way. Many critical situations, which formerly might have led to discharge against medical advice, are now handled more realistically and sympathetically *on the wards*, using many of the same techniques as those used on the special ward.

Certain factors are regarded as essential for the successful operation of this type of special discharge ward procedure:

Active support by the hospital staff is necessary: Orientation of the entire staff in the methods and goals of such a procedure, in realization of the inadequacy of older methods, and the need for active cooperation, is essential. It is understandable that some ward physicians prefer to have patients discharged *directly* from their wards. Not uncommonly, a patient's leaving against medical advice carries for the doctor an implication that he has failed in some way to handle the treatment situation properly. To achieve the best cooperation, it is necessary to avoid making the ward doctor feel that, after he has "failed," someone else is taking over to make things "right." Rather, he should be helped to see that he is part of a team and that it is to be expected that he will have to call for the help of the team in certain situations.

Cooperation among the special ward staff is equally essential. The doctor, nurses, and aides can present a united front in helping the patient to stay in the hospital or they can nullify each other's efforts. Little is achieved if one pacifies the patient while another riles him. Nor does it help if the clothing man delivers the patient's street clothes at the point where the social worker has almost persuaded the patient to stay. Good communication is necessary among the team members, and someone has to "call the signals." In this hospital, the special ward physician has acted in this capacity and "captained" the team.

The procedure must be uniform for all patients: This should be a regular procedure established by the hospital administration. If it breaks down for one patient, other patients may refuse to cooperate or they may feel that they are being treated unfairly. Unless it is routine, there may be temporizing and evading on the part of the staff.

A separate room must be set aside and designated as the special ward: The patient should be removed from the emotionally involved setting in which he demanded his discharge. By so doing, he may "cool down" and view the situation objectively. It also reduces the patient's feeling of bravado which may result from his defiance of authority before his fellow patients and minimizes the feeling of desperate adherence to a stand. Otherwise, he is "out on a limb" from which he cannot retreat without "losing face." Leaving his ward tends to confront him with the fact of his dependency on the hospital, but it also gives him the feeling that he is on his way out so he doesn't need to fight the hospital.

The members of the Psychosomatic Department of this hospital took an active role in establishing this procedure. They solicited the cooperation of the staff and the administration, and were instrumental in setting up the machinery by which the procedure functions. However, the success and continuation of the procedure have been due largely to the efforts of the *entire* staff and particularly to the special ward doctor. Whatever professional skills are available should be utilized to full advantage. Such a procedure can be established in any hospital in which

the staff is interested and willing. This type of special discharge ward procedure is particularly applicable to larger hospitals where the relationship between patient and physician is of necessity more formal and impersonal. In smaller sanatoriums, many of the techniques of this procedure are a natural part of the patient's milieu.

There are limitations to the procedure; all patients cannot be "retrieved." Most of those who attempt to leave are difficult to deal with. When they remain, the wards to which they return may become more highly charged emotionally. Herein the mental health of the hospital staff is reflected: How much disturbance to the peace and quiet of the ward can be tolerated? Everyone needs to feel that his efforts are appreciated. It seems quite natural not to object too vigorously if disgruntled and unappreciative patients threaten to leave. If a ward doctor sends one or two patients to the special ward, and they leave, he is likely to conclude that the procedure is not of much help. His enthusiasm and cooperation tend to wane. It is important, therefore, to keep the staff apprised of the successes of the method and of reductions in the rate of discharges against medical advice.

This special discharge ward procedure is expensive in staff hours devoted to special attention to "uncooperative" patients. However, it should be pointed out that considerable time and effort had been expended previously in dealing with this same type of patient on the ward level. Probably no more staff time is required with the special ward, but it is used in a more concentrated and effective manner.

A further problem is related to the possibility that some patients will utilize the ward procedure to obtain special privileges. One example of this, in our experience, has been in relation to passes. If patients believe that threatening to leave against medical advice and going to the special ward is a means of obtaining a pass or leave, many will request such a discharge. After the first 2 patients who received passes from the special ward failed to return to the hospital, it became the policy of our hospital not to issue any passes or leaves from the special ward. However, an occasional patient reveals information on the special ward explaining his desire to leave which makes it reasonable or imperative that he be allowed to take care of matters outside the hospital. In such cases the (original) *ward doctor* is advised of the situation. If he decides that the patient's medical condition permits an emergency pass, the patient is transferred back to his ward and the pass is granted.

Another example of misuse of the special discharge ward is in regard to interward transfers. The system is abused if the patients feel that the procedure is a convenient method of transferring to a ward where "the grass may look a little greener." Generally, our policy has been to return a patient to the ward from which he came. Rarely, a patient may be quite disturbed by certain personnel or patients on a particular ward and express the belief that he could continue with hospitalization on another ward. In such cases, objective inquiry is made and the sincerity of the patient is evaluated. His own ward doctor is consulted. With consensus established the patient may be transferred to a new ward.

Changing wards may at times be therapeutic to the doctor as well as to the patient. However, this special discharge procedure does not enable a doctor to transfer all his "problem patients" away from his ward. Ward doctors *receive* patients from the special ward as well as send them there.

The discharge procedure broke down at times, and efforts were made to find the reasons. In one case a nonpsychotic patient was threatening and had a knife. He was allowed to leave by whatever route he chose. In 3 cases, the demands to leave were made on week-ends and the procedure was not yet well enough organized to function properly, with a number of the staff members off duty. Since then, minimum coverage of the special ward has been arranged at all times. It is reassuring to note that these few exceptions did not disrupt the procedure for other patients.

Although it is impossible to tease out the effect of a single factor, it is our conclusion that the decrease in the rate of discharge against medical advice and parallel reduction in irregular discharge rate of this hospital have been due to a considerable extent to the effect of the special discharge ward procedure. There are three grounds on which this conclusion may be challenged.

First, the procedure may merely effect a conversion of discharges against medical advice to absent-without-leave discharges. If a large number of discharges against medical advice simply had been converted to absent-without-leave discharges, the ratio of irregular discharges to maximum-hospital-benefit discharges should have remained approximately the same. As the rate of discharge against medical advice decreased, the absent-without-leave rate should have increased proportionately. In fact, the number of absent-without-leave discharges did increase, but the ratio of such discharges to maximum-hospital-benefit discharges has remained constant: approximately 1 to 5 both before and after the special ward opened. Thus, the *total* irregular discharge rate *decreased* along with the rate of discharge against medical advice.[7]

A second criticism against the inference that the institution of the special ward is largely responsible for the reduction is to the effect that a "maturation" of the patient population has occurred and has been responsible for the reduction in discharges against medical advice. The hospital is relatively new and only recently has been filled to capacity. Accordingly, the marked increase in maximum-hospital-benefit discharges during the past year probably is a reflection of

[7] In the year since the special ward has been in operation, there has been a larger proportion of absent-without-leave discharges from the "bed-rest" wards. Twenty-three of the 51 absent-without-leave discharges during this year occurred among patients who had not yet reached the rehabilitation phase of their treatment. In the preceding year, only 5 of 27 absent-without-leave discharges occurred among patients from the "bed-rest" wards. An explanation of this may be that the pass policy of the hospital has been somewhat more liberal during the past year. In view of this, it may be that a few patients on the "bed-rest" wards have received passes and failed to return who would previously have been unable to get a pass and might have left against medical advice. The results show that absent-without-leave and against-medical-advice discharges are *now* of about equal magnitude in this hospital. Accordingly the absent-without-leave discharge problem is presently under investigation.

the "maturing" hospital population: more and more patients have completed treatment. However, it is not tenable that the decrease in the rate of discharge against medical advice is solely a reflection of the increased number of maximum-hospital-benefit discharges. The reduction in discharges against medical advice is absolute, not just in relative per cent. It may be noted in figure 3 that the numbers of both against-medical-advice and the maximum-hospital-benefit discharges increased during the year preceding the inauguration of the special ward procedure, but the number of discharges against medical advice *decreased* sharply in the following year while maximum-hospital-benefit discharges continued to increase.

Another possible criticism is that consolidation of the staff of this new hospital has been responsible for the reduction in discharges against medical advice. As time passes in a new hospital and the "shake-down" period is over, a consolidation of the staff occurs. It might be argued that this is the reason for the decrease in discharges against medical advice, and that the special ward procedure was just incidental. If this were the case, the growth of organization and group solidity being a gradual process, the reduction in discharges against medical advice also should have been gradual. From study of figure 3, it is evident that this did not happen. Instead, a sharp decrease occurred immediately following the inauguration of the special ward procedure. In addition, it is known that a number of well-established tuberculosis hospitals with a stable staff and patient population continue to have a high rate of discharge against medical advice.

It is not proposed that this special discharge ward procedure is *the* answer to the irregular discharge problem. It has been effective, however, in "retrieving" patients who would otherwise have left the hospital by discharge against medical advice and it has played an important part in decreasing by more than half the rate of discharge against medical advice.

SUMMARY

This communication is a preliminary report based on twelve months' experience with a special discharge ward procedure designed for reducing discharges against medical advice.

During the first six months, 24 patients were admitted to this ward. Sixteen of these patients were "retrieved." During the twelve-month period after inauguration of this special discharge procedure, the rate of discharge against medical advice from the hospital decreased from 36 to 15 per cent of discharges, and the total irregular discharge rate fell from 52 to 34 per cent.

Various aspects of the development and operation of this special discharge procedure are discussed, as well as the results, both direct and indirect.

SUMARIO

Investigación de las Altas Dadas Irregularmente a Tuberculosos: Procedimiento Especial en las Salas para Disminuir las Altas Dadas contra Dictamen Médico

Esta comunicación preliminar se basa en la experiencia obtenida en doce meses con un procedimiento especial utilizado en las salas de hospital con mira a disminuir las altas dadas contra el consejo del médico.

Durante los primeros seis meses, se recibieron 24 enfermos en la sala en cuestión. Dieciséis de esos enfermos fueron "rescatados." Durante el período de doce meses consecutivo a la instalación de estre procedimiento especial de altas, el coeficiente de altas contra dictamen médico en el hospital descendió de 36 a 15 por ciento de las altas y el coeficiente total de altas irregulares bajó de 52 a 34 por ciento.

Se discuten varios aspectos del desarrollo y funcionamiento de este procedimiento especial para altas, y también los resultados, tanto directos como indirectos.

RESUME

Départ irrégulier du tuberculeux hospitalisé: Un procédé spécial pour réduire les départs non autorisés médicalement

Cette communication constitue un rapport préliminaire fondé sur douze mois d'expérimentation dans un service d'une méthode spéciale destinée à réduire le nombre des départs de l'hôpital non autorisés médicalement.

Au cours des six premiers mois, 24 patients ont été admis dans ce service. Seize d'entre eux ont été "récupérés". Au cours de la période de douze mois succédant à l'institution de ce procédé spécial pour les "sorties", le taux des départs non autorisés médicalement est descendu, dans ce service, de 36 à 15% pour la totalité des sorties et le taux des départs irréguliers est passé de 52 à 34%.

Divers aspects du développement et de la mise en oeuvre de ce procédé spécial applicable aux "sorties" et les résultats directs et indirects qu'ils entraînent sont commentés.

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THE COURSE OF IDIOPATHIC PLEURAL EFFUSION IN FIFTY PATIENTS[1]

JOSEPH T. SKAGGS[2] AND GEORGE W. SMILEY

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INTRODUCTION

A review has been made of the course of the patients discharged during the years 1939 to 1952, inclusive, from the State Sanatorium for Diseases of the Chest at Oakdale, Iowa, with an established diagnosis of idiopathic pleural effusion. This hospital has 425 beds and is the only state-supported hospital devoted exclusively to the diagnosis and treatment of diseases of the chest. There are six other sanatoriums for chest disease in the state supported by counties in which large cities are located. Therefore most of the patient population of the Oakdale institution is derived from the rural area of the state.

In the analysis, only cases which satisfied the usual definition of idiopathic pleural effusion were included. Excluded were the cases of patients with any evidence of parenchymal, endobronchial, or extrapulmonary tuberculosis. Other causes of pleural effusion were excluded. If a parenchymal lesion was discovered on a post-thoracentesis roentgenogram, the patient was excluded from the series.

OBSERVATIONS

General characteristics of group: Fifty patients were found who fulfilled the criteria established for this study. With the exception of 2, all were born in Iowa, Illinois, Missouri, Wisconsin, Minnesota, and Indiana. One patient was born in Norway and the other in Sweden, but both had resided in Iowa for a number of years. There were no Negroes, Orientals, or American Indians. Among the patients studied, one patient was of Mexican ancestry.

Of the 50 patients, 28 were men and 22 were women. The youngest patient was fifteen years of age and the oldest, sixty-three.Nine patients were less than twenty years of age. There were 20 patients from twenty to twenty-nine years old, 9 patients in their thirties, 5 in their forties, and 7 were fifty years or older. The greatest number of patients were in the second and third decades, but 24 per cent of the entire group were more than forty years of age. Twenty-two patients were single and 28 were married.

Exposure to tuberculosis: A definite familial or contact history of tuberculosis was established in 18 of the 50 patients with pleural effusion. Among the 18 were four physicians and nurses who had had contact with tuberculous patients.

Clinical manifestations: The duration of symptoms of pleural effusion was from three days to one year. One third of the patients had symptoms for one month or less; another third from one to three months; and the remaining dated

[1] From the Department of Internal Medicine, State University of Iowa, Iowa City; and the State Sanatorium for Diseases of the Chest, Oakdale, Iowa.

[2] Present address: 815 Atlas Building, Charleston 1, West Virginia.

the onset of their symptoms over three months. The most common complaint which occurred in 44 of the 50 patients was chest pain; always on the same side as the effusion. Thirty-seven patients had or had had fever and 33 of the 50 had a cough. The cough was described as being uniformly mild. From what could be derived from the clinical records, only 5 of the 50 patients had truly productive coughs. Two patients described blood-streaked sputum but there were no frank pulmonary hemorrhages. Weight loss had been sustained by 33 patients but anorexia was reported by only 21 of the 50. Night sweats were reported by 18 of the group. The incidence of these complaints agrees well with the experience of Karron and Purves (1).

It is important to note that none of these patients was discovered in mass survey roentgenograms, pre-employment examinations, or other incidental studies. Without exception, each consulted his physician because of specific complaints.

Roentgenography: Roentgenograms of the chest revealed evidence of definite pleural effusions in all of the patients. The left side of the chest was involved in 58 per cent of the patients and the right in 42 per cent. There were no bilateral effusions.

Tuberculin reaction: The intracutaneous (Mantoux) test for tuberculosis, utilizing Old Tuberculin (OT), is used routinely at the State Sanatorium. However, this test was recorded in only 38 of the 50 patients. All of the 38 tests were recorded as positive.

Characteristics of the fluid: The effusions which were aspirated and described adequately had the characteristics of an exudate. One patient was found to have had bloody fluid on two occasions and, interestingly enough, he was recently readmitted to the State Sanatorium, six years after the onset of his effusion, with far advanced pulmonary tuberculosis. It must be pointed out that in a number of patients the effusion had receded to an extent which precluded thoracentesis.

Bacteriologic findings: According to Barnwell (2) at least 70 per cent of pleural effusions of the so-called idiopathic type can be proved to be tuberculous by adequate examination (including repeated culture and guinea pig inoculation) of the sediment of 100 to 500 ml. of fluid. In the present series, the aspirated fluids of 29 patients were studied by culture, guinea pig inoculation, or both. Tubercle bacilli were cultured from 7 of the 29 patients with pleural fluid available for study. Four of these patients whose pleural fluid was sterile on culture for tubercle bacilli were proved to have tuberculosis by other means at a later date.

Even with repeated examination of the sputum with stain and culture, *Mycobacterium tuberculosis* was not found in the sputum of any patient in the initial sanatorium examination. Likewise, all cultures of the gastric contents were negative. Forty-five patients (90 per cent) had an elevated erythrocyte sedimentation rate on admission. Except for 2 patients with mild hypochromic anemia, the routine blood counts and urinalyses done on admission were not remarkable. No cultures of the urine were made unless genitourinary tuberculosis was suspected clinically. Other diseases diagnosed in the patients are shown in table 1.

Therapy: The treatment program for all of these patients consisted of strict

TABLE 1

OTHER DISEASES DIAGNOSED IN FIFTY PATIENTS WITH IDIOPATHIC PLEURAL EFFUSION

Chronic purulent sinusitis
Allergic rhinitis
Bronchial asthma, extrinsic
Diabetes mellitus
Rheumatic heart disease (mitral insufficiency)
Psoriasis
Late latent syphilis (3)
Reactive depression
Essential hypertension
Cystic disease of the breast
Rheumatoid arthritis, inactive

bed rest until the fluid receded, and then graduated exercises were given. The patients with authorized discharges from the sanatorium remained for an average of 370 days. Those who were discharged against medical advice were hospitalized for an average of 201 days. The fact that 54 per cent of the entire group left the hospital without authorization attests to the benign nature of the disease, as interpreted by the patient.

Course subsequent to pleural effusion: An attempt was made to learn the subsequent course of all of the 50 patients by a personal letter to each. To date, follow-up observations, consisting either of replies to the letter or a clinic examination have been obtained for 42 of the 50 patients. Thirty-four are living and well, 3 are living with tuberculous complications, and 5 are dead.

Five of the patients in the series were readmitted to this hospital within six years after their original admission with a pleural effusion. Two of the 5 patients had disseminated tuberculosis; one patient had a minimal pulmonary lesion, tuberculous laryngitis, and renal tuberculosis; one patient had tuberculous epididymitis and subsequent involvement of the inguinal nodes; and one patient had far advanced pulmonary tuberculosis.

Five patients in the series have died, a case mortality rate of 10 per cent. All of the 5 patients died of disseminated tuberculosis within six years of their initial hospitalization for so-called "idiopathic" pleural effusion. In only 2 of the 5 patients who died were tubercle bacilli cultured from the aspirated effusion on the initial hospitalization. The pleural fluid in one patient was found to be negative for tubercle bacilli. The other 2 patients did not have thoracentesis because of the resorption of the fluid.

Fatal cases: Brief case resumés of the patients who died follow:

Case 1. W. M. was a 27-year-old white farmer with no contact history of tuberculosis. He complained of left chest pain, cough, fever, night sweats, and an 18-pound weight loss for four months. Thoracentesis was not done because of resorption of fluid. All studies were negative except the tuberculin reaction (Mantoux), which was positive. He had an uneventful hospitalization for seven months and then manifested signs of tuberculosis of the spine, meninges, and sternum. He died 400 days after admission.

Case 2. B. T. was a 25-year-old white housewife whose husband had pulmonary tuberculosis. She gave a history of only left-sided chest pain for five weeks. No thoracentesis was done

because of rapid resorption of a pleural effusion which was discovered. After 198 days she left the sanatorium against advice. She died elsewhere two years later of disseminated tuberculosis. (The tuberculin test was not recorded in this case.)

Case 3. O. J. was a 37-year-old laborer whose grandmother died of tuberculosis. He was admitted in 1941 with a history of chest pain, "chest cold," shortness of breath, cough, and 28-pound weight loss. The pleural effusion which was found on admission to the hospital was negative for tubercle bacilli on culture. All other studies were negative except the tuberculin reaction, which was positive. After 204 days he left the sanatorium against advice. He was readmitted five years later with disseminated tuberculosis and tubercle bacilli in the sputum. He died 16 months after his second admission.

Case 4. D. M. was a 52-year-old mortician with no family history of tuberculosis. At the time of hospital admission for the pleural effusion, he gave a history of a chronic upper respiratory infection, fever, fatigue, slightly productive cough, and a 25-pound weight loss. Two cultures of aspirated fluid were positive for tubercle bacilli. The fluid persisted but the patient's general condition was satisfactory. He left the sanatorium against advice after 474 days of hospitalization. On readmission in four months he was found to have tuberculosis of the thoracic spine. Subsequently he developed a cold abscess, transverse myelitis, and other lesions of disseminated tuberculosis. Death occurred two and a half years after the second admission.

Case 5. L. B. was a 40-year-old grain processer whose brother and sister had tuberculosis. He had had "pneumonia" four months prior to admission and his chest was aspirated at that time because of fluid. No studies were done. After this illness he had a fever, left chest pain, dry cough, and a 6-pound weight loss. He was admitted with a massive left pleural effusion. Examination of the sputum and gastric contents were negative but the aspirated effusion contained tubercle bacilli. The effusion receded and the patient appeared to be doing well. Approximately 100 days after admission he developed a high fever and about seven days later showed signs of miliary tuberculosis. The sputum became positive for tubercle bacilli 4 days before death which was 19 days after the onset of the fever.

DISCUSSION

The present report concerns 50 patients who could be described as having "benign idiopathic pleural effusion" on admission to a state tuberculosis sanatorium. Although this study embraces the population of a sanatorium, it is believed that these 50 patients are entirely representative of those seen in private practice or in general hospitals. Most were referred directly to the sanatorium by their private physicians without hospitalization elsewhere. At first sight, there was no evidence identifying these patients as tuberculous.

No attempt has been made to evaluate treatment, e.g., duration and quality of bed rest, in terms of final outcome.

The ominous nature of so-called idiopathic pleural effusion is borne out by the observation that 8 patients developed serious forms of tuberculosis from six months to six years after the onset of their effusions. Five of these 8 patients are known to have died from disseminated tuberculosis. Moreover, 7 of the 8 patients who developed further manifestations of tuberculosis developed extrapulmonary disease as well as the pulmonary form. Only one patient has had pulmonary tuberculosis as an apparently localized process. This finding supports the opinion that pleural effusion is part of the picture of disseminated tuberculosis.

The case mortality observed in the present study is somewhat surprising be-

cause the patients reported here were from presumably favorable rural environments. With a single exception they were not from socio-economic or cultural groups which are supposedly more susceptible to tuberculosis. Furthermore, an unusual effort has been made to limit the selection to those patients who had only pleural effusion at the time of the original diagnosis.

The present results give additional support to the belief that the patient who develops a pleural effusion for which no other cause can be found must be considered tuberculous and given appropriate treatment. This, of course, includes a long range follow-up program. In addition, a careful search for all possible foci of tuberculosis should be made in all such patients.

SUMMARY

Fifty patients with so-called "idiopathic pleural effusion" have been studied. The clinical features presented by these patients are outlined.

Twenty-nine patients had aspirated fluid examined for tubercle bacilli by culture, guinea pig inoculation, or both. Only seven diagnoses of tuberculosis were made by these methods. It is believed that tubercle bacilli would have been found more often if more cultures of larger quantities of fluid had been made.

Follow-up studies have been completed in 42 of the 50 patients in the series. The cumulative incidence of tuberculosis was found to be 16 per cent; and 5 patients have died, thus making a case mortality rate of 10 per cent. The fact that each of these patients consulted his physician because of specific complaints shows again the important role of the family physician in tuberculosis case finding.

It is the opinion of the writers that idiopathic pleural effusion is almost invariably a manifestation of tuberculosis and should be so treated.

SUMARIO

La Evolución del Derrame Pleural Idiopático en Cincuenta Enfermos

Este estudio comprendió a 50 enfermos que padecían del llamado "derrame pleural idiopático." Bosquéjanse las características clínicas presentadas por estos sujetos.

En 29 enfermos, se examinó el líquido aspirado en cultivos, inoculación en el cobayo o de ambos modos. No se hicieron más que siete diagnósticos de tuberculosis con estos métodos. Parece que se hubieran encontrado bacilos tuberculosos más a menudo si se hubiesen hecho más cultivos de cantidades mayores de líquido.

En 84 por ciento de los enfermos de la serie, se llevaron a cabo estudios subsiguientes. La incidencia acumulativa de tuberculosis resultó ser de 16 por ciento; y la mortalidad por tuberculosis, 10 por ciento. El hecho de que cada uno de estos enfermos consultó al médico debido a síntomas específicos demuestra de nuevo que el médico de la familia es el "diente" principal en el engranaje que lleva al descubrimiento de casos de tuberculosis.

Opinan los AA. que el derrame pleural idiopático es una manifestación de tuberculosis y así debe tratarse.

RESUME

Le cours de l'épanchement pleural idiopathique chez cinquante malades

Cinquante malades atteints de ce que l'on appelle "épanchement pleural idiopathique" ont été étudiés. Les signes cliniques présentés par ces malades sont décrits.

Chez vingt-neuf malades le liquide de ponction a été examiné par la culture, l'inoculation au cobaye ou les deux.

Par ces méthodes 7 diagnostics de tuberculose seulement ont été obtenus. On croit que les bacilles tuberculeux auraient été trouvés plus souvent si un plus grande nombre de cultures avait été effectué avec des quantités de liquide plus grandes.

Chez 84 pour cent des malades de cette série, les observations ont pu être poursuivies. L'incidence cumulative de la tuberculose constatée s élève à 16 pour cent et la mortalité par tuberculose à dix pour cent. Le fait que chacun de ces patients avait consulté son médecin pour des manifestations pathologiques spécifiques montre de nouveau que c'est le médecin de famille qui, dans le rovage du dépistage de la tuberculose représente l'engrenage essentiel.

Les auteurs considèrent que l'épanchement pleural idiopathique est une manifestation de la tuberculose et doit être traité comme telle.

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Case Reports

FATAL TUBERCULOUS MENINGITIS DEVELOPING DURING ISONIAZID-STREPTOMYCIN THERAPY[1]

ROGER S. MITCHELL, LEIGHTON ANDERSON, IRVING OHR, AND GARDNER MIDDLEBROOK

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The purpose of this report is to describe the clinical course and pathologic and microbiologic findings in a case of tuberculous meningitis which first appeared and progressed to fatal termination in a patient under treatment with isoniazid and streptomycin.

CASE REPORT

R. W., a 36-year-old white machinist, was admitted to the hospital on November 3, 1954, for right pneumonectomy for pulmonary tuberculosis. He was well until 1945 when he noted a rather rapid onset of chills, fever, night sweats, right-sided pleuritic pain, cough, expectoration, and loss of 20 pounds. He had been exposed to another sailor in the Merchant Marine who later died of tuberculosis. The patient had had a normal chest roentgenogram in 1942. The diagnosis of tuberculosis was confirmed by finding a cavity in the right lung and acid-fast bacilli in the sputum. He rested at various hospitals for two years; the right lung was treated with artificial pneumothorax and, later, a phrenic nerve interruption. He did well, with rather prompt relief of his symptoms, and tubercle bacilli disappeared from the sputum. The patient was then fairly well until 1949 when pneumothorax refills were stopped because the space was being lost. The sputum was then found to contain acid-fast bacilli. At this time he rested eleven months and received streptomycin, 1 gm. per day intramuscularly, for ninety days, with apparently satisfactory results.

The patient was then well until April, 1953, when he had his first hemoptysis; he also noticed an anal fistula, cough, expectoration, and weight loss. He came to Denver where six sputum examinations were negative for tubercle bacilli in January, 1954. In May, 1954, following another hemoptysis and a "spontaneous collapse" of the right lung, he was readmitted to a sanatorium. *M. tuberculosis* was cultured from both sputum and chest fluid at this time. Pus was aspirated from the right chest; his doctor told him he had "empyema with bronchopleural fistula." On May 18, the patient was placed on streptomycin, 1 gm. twice weekly, and isoniazid, 300 mg. daily (approximately 5 mg. per kg.) which were continued without interruption thereafter. (His only previous tuberculosis chemotherapy had been for ninety days in 1949, when he had received streptomycin.) Sputum was soon negative for acid-fast bacilli, but the chest fluid remained intermittently positive for *M. tuberculosis* (table 1).

The patient had had poliomyelitis when he was six years old, since which time he has had weakness of both legs. Review of systems was otherwise noncontributory.

On admission he was a thin, chronically ill-appearing man with signs of right pyopneumothorax, bilateral leg and right shoulder muscle weakness, and atrophy. Bronchoscopy on November 24, 1954, showed inflammation and granulations in the right upper lobe orifice and narrowing of the right bronchus intermedius. On December 8, a right pneumonectomy was performed without incident; his postoperative course was rather stormy, with temperature elevation of 102°F., and pulse ranging between 100 and 120 per minute. There was a

[1] From Colorado General Hospital, Colorado Foundation for Research in Tuberculosis, National Jewish Hospital, and University of Colorado School of Medicine, Denver, Colorado.

TABLE 1

BACTERIOLOGIC FINDINGS: SPUTUM AND CHEST FLUID

Date	Source of Specimen	Tuberculous Bacteriologic Findings	
		Smear	Culture
11-3-54	Sputum	+	—
11-5-54	Sputum	+	—
11-8-54	Sputum	+	0
11-24-54	Bronchial washings	0	0
12-13-54	Chest fluid	0	0
12-15-54	Sputum	0	—
12-20-54	Chest fluid	—	+
12-23-54	Chest fluid	0	+
1-20-55	Chest fluid	—	0
2-17-55	Chest fluid	0	0
3-1-55	Sputum	0	—
3-2-55	Sputum	0	—
3-3-55	Sputum	0	Contaminated

+ = positive
0 = negative
— = not done

new shadow in the left lower lung field on the fifth day which persisted without change throughout the balance of his course. Serosanguineous fluid was aspirated from the pneumonectomy space on the third day; this became purulent on the ninth day. Approximately six weeks after operation, tube drainage through a rib resection was performed because of fever, prostration, and bacteriologic evidence of mixed-infection empyema.

The patient then seemed to do moderately well until March 13, 1955, approximately three months after the pneumonectomy, when he first complained of headache and manifested some personality change and an intermittent low fever. A diagnosis of tuberculous meningitis was made five days later on the basis of cerebrospinal fluid findings (table 2). The isoniazid was immediately increased to 600 mg. per day (approximately 10 mg. per kg.) and streptomycin was increased to 1 gm. per day. His course was slowly downhill during the next five weeks. Bacteriologic confirmation of the diagnosis was not obtained until after death. Six days before death, the daily intrathecal administration of 50 mg. of streptomycin was started. Two days before death streptomycin was stopped and pyrazinamide, 3 gm., and para-aminosalicylic acid (PAS), 12 gm., a day were added to the isoniazid with no apparent benefit. The patient died on April 23, 1955.

Brief Summary of Post-Mortem Findings[2]

The brain weighed 1,400 gm. The meninges over the base of the brain about the optic chiasm and the inferior surface of the pons had a thick gelatinous purulent exudate. The convolutions were flattened and the meninges were congested and edematous. The ventricles contained a slightly turbid fluid and their walls were soft and granular. The right lung was absent and the parietal pleura was thick, rough, friable, and green. A small amount of seropurulent fluid was present in the dependent portion of the cavity about the two drains. The right bronchial stump was intact but showed granulations. The left pleural cavity was obliterated by firm visceral and parietal adhesions. On cut surface, the left lung contained

[2] Performed by Dr. J. K. Lowry, Department of Pathology, University of Colorado School of Medicine, to whom the writers are indebted for this report.

TABLE 2

CEREBROSPINAL FLUID FINDINGS

Date	Initial Pressure	Sugar	Protein	Chloride	Cells		Tuberculous Bacteriologic Findings	
					Number	Per Cent Lympho-cytes	Smear	Culture
3-17-55	400	57	180	116	100	80	—	—
3-18-55	—	57	180	110	140	100	0	+
3-19-55	—	73	189	111	140	100	—	+
3-21-55	—	36	141	115	129	100	0	0
3-22-55	—	—	—	—	—	—	0	+
3-23-55	—	—	226	—	71	87	0	+
3-28-55	—	27	196	106	202	98	0	0
4-2-55	—	19	319	99	5	20	—	—
4-7-55	275	37	371	96	94	69	—	+
4-15-55	270	43	684	92	120	90	0	+
4-19-55	—	58	309	87	36	52	0	—
4-20-55	—	62	360	85	70	74	0	—
4-21-55	—	66	371	80	6	100	0	—

0 = negative
+ = positive
— = not done

numerous nodules, some of them with necrotic centers. The lung weighed 800 gm. and contained numerous emphysematous blebs. A copious amount of bloody red fluid exuded from the cut surface. In the superior portion of the left upper lobe was a 6 mm. cavity with dark black borders. The mediastinal lymph nodes were slightly enlarged and gray-black. The mesentery and omentum contained numerous miliary 1 to 2 mm. gray caseous nodules and enlarged soft gray-yellow lymph nodes. The liver weighed 2,700 gm.; in the left lobe were several 1.5 cm. tan focal areas which stood out in contrast to the dark purple surrounding area.

The meninges were infiltrated with lymphocytes, plasma cells, macrophages, and neutrocytes. Much caseous necrosis was also present, containing numerous acid-fast bacilli. The adventitia and media over many of the arteries and veins were infiltrated with lymphocytes and neutrocytes. The left lung contained several nodules composed of necrotic centers surrounded by epithelial cells, fibroblasts, fibrous connective tissue, and an outer zone of lymphocytes. Some of the necrotic centers contained basophilic amorphous material while others contained granulation tissue. Numerous nodules of non-necrotic fibrillary fibroblastic granulation tissue were also present. The central veins and radiating sinusoids of the liver were dilated and filled with blood. Some of the adjacent liver cord cells were atrophic and had large ghostlike nuclei. Small groups of lymphocytes and a few neutrocytes spilled over from the sinusoids into the cord cells. A similar infiltrate was present in the portal spaces. The miliary nodules in the mesentery and omentum were small granulations with a rare giant cell, well surrounded by fibroblasts.

Final Diagnosis

1. Tuberculosis: (*a*) meninges, acute; (*b*) lung, left, advanced; (*c*) bronchus, right; (*d*) spleen, capsule; (*e*) mesentery and omentum, miliary; (*f*) lymph nodes, pulmonary and mesenteric
2. Wound, skin, chest, right, surgical, partially healed: (*a*) absence, lung, right, surgical
3. Hepatitis, focal, acute, nonspecific

4. Poliomyelitis, chronic, old (clinical): (*a*) curvature, spine, thoracic, left; (*b*) atrophy, muscle, both lower extremities, and right shoulder girdle.

Studies on the Tubercle Bacilli Isolated at Necropsy

A fragment (approximately 500 mg.) of inflammatory granulation tissue was removed from the base of the brain at necropsy. It was emulsified aseptically into a fine suspension in 10 ml. of sterile 0.2 per cent bovine albumin in distilled water in a Teflon®-glass grinder (1). Ziehl-Neelsen stained smears of this material revealed approximately one acid-fast rod per oil immersion field. This suspension was divided into two equal aliquots, one of which was exposed to an equal volume of alkali (1.0 N sodium hydroxide containing 0.1 N trisodium phosphate) for thirty minutes, centrifuged, neutralized, and resuspended in 0.2 per cent sterile albumin solution; the other aliquot was used without "decontamination." Both the decontaminated and the untreated suspensions were inoculated in duplicate and in 0.2 ml. volumes at 10^0, 10^{-1}, and 10^{-2} dilutions in 0.2 per cent sterile bovine albumin on to quadrants of Felsen plates containing a modified oleic acid–albumin agar medium as previously described (2). This method permits direct drug-resistance testing. The plates were incubated for twenty-one days at 37°C. and the culture, drug resistance, and catalase activities of the bacilli isolated were examined at the end of this period. The results are recorded in table 3.

The bacilli isolated were human tubercle bacilli by all criteria: cellular morphology, colonial morphology, cord formation, slow growth rate, and absence of pigmentation. It was evident that only one-third to one-half of the population of bacilli were resistant to as little as 1 γ of isoniazid per ml., and that all colonies were catalase positive. No catalase-negative mutants were present in the entire population isolated.

Three colonies of tubercle bacilli were also isolated from a decontaminated suspension of fragment of omentum which contained a few miliary tubercles. These organisms were not submitted to further study except to catalase testing: all three colonies were catalase positive.

Further bacteriologic and pathogenetic studies have been initiated on the tubercle bacilli isolated from the brain at necropsy, with the application of airborne infection techniques, as previously described (6).

TABLE 3

PRIMARY ISOLATION OF TUBERCLE BACILLI FROM INFLAMMATORY TISSUE AT BRAIN BASE
Results of Culture, Drug Susceptibility, and Catalase Tests

Material Cultured	Dilutions of Tissue Suspensions											
	10^0 (Undiluted)				10^{-1}				10^{-2}			
	No drug	2.5 SM*	1 INH	10 INH	No drug	2.5 SM	1 INH	10 INH	No drug	2.5 SM	1 INH	10 INH
Untreated suspension	Innum.	0	Innum.	0	Innum.	0	Innum.	0	345†	Many	146	0
									259	small	149	
	Cat. + + +	—	Cat. + +	—	Cat. + + +	—	Cat. + +	—	Cat. + + +	Cat. + +	Cat. +	—
Decontaminated suspension	Innum.	Few small	Innum.	0	Many	0	Many	0	23	0	6	
									32		12	
	Cat. + + +	—	Cat. + +	—	Cat. + + +	—	Cat. + +	—	Cat. + + +	—	Cat. +	—

* Concentrations of drugs are in γ per ml. of oleic acid–albumin agar medium.

† Actual colony counts, in duplicate.

SM = streptomycin; INH = isoniazid; Innum. = innumerable colonies; Cat. = catalase test result

DISCUSSION

Two other cases of interest in this connection have come to our attention. Schwartz (3) described a 34-year-old Negro male with pulmonary tuberculosis for several years who developed headache and stiff neck on December 12, 1954; he was found three days later to have cerebrospinal fluid findings consistent with a diagnosis of tuberculous meningitis. Chemotherapy including isoniazid, PAS, and streptomycin had been given off and on since March, 1951. Isoniazid, 300 mg. a day, and streptomycin, 1 gm. twice weekly, had been resumed October 11, 1954. An apical posterior segmental resection of the left upper lobe had been performed on November 19, 1954, to remove a large caseous nodule. After meningitis was diagnosed, chemotherapy was changed to viomycin, 1 gm. twice weekly; isoniazid, 600 mg. daily; and pyrazinamide, 3 gm. daily, on December 15, 1954. Isoniazid was discontinued on February 7, 1955, because of acute mental symptoms; these symptoms then promptly subsided. The cerebrospinal fluid bacteriologic findings were negative throughout and the fluid was entirely normal by February 3, 1955. The patient left the hospital against advice soon thereafter.

Smith (4) described a second case, a 58-year-old Negro male with far advanced tuberculosis diagnosed in January, 1954. Streptomycin or dihydrostreptomycin, 1 gm. twice weekly, plus isoniazid, 300 mg. a day, were given from February 1, 1954, to December 11, 1954, and then stopped because of stiffness, weakness, and pain in hands and feet and some mental confusion. Because mental confusion became worse and a facial paralysis appeared, the cerebrospinal fluid was examined on January 10, 1955, and February 24, 1955; the findings were quite consistent with a diagnosis of tuberculous meningitis but without bacteriologic proof, then or later. Streptomycin, 1 gm., and isoniazid, 300 mg., each daily, were resumed on January 7, 1955. By April 1, 1955 all abnormal symptoms and physical findings indicative of meningitis had disappeared.

It should be stressed that this second case may have occurred at least in part because of cessation of chemotherapy on December 11, 1954, occasioned by presumed isoniazid toxicity. Furthermore, neither of these two patients was proved bacteriologically to have tuberculous meningitis and both have made apparent rapid recoveries; the first, possibly because of the addition of viomycin and pyrazinamide to the therapeutic regimen.

To the present writing, no case of tuberculous meningitis has been reported as developing and progressing to death in a patient being treated with isoniazid. The fact that, in the case reported here, the microbial agents of the progressive meningitis were typical human tubercle bacilli which were only weakly resistant to isoniazid and were catalase positive seems especially significant. It has previously been reported that such mutants are only slightly to moderately attenuated for guinea pigs (5, 6); and it was anticipated that such strains might certainly behave as agents of progressive tuberculous disease in man (2, 7). It has also been pointed out that only with doses of isoniazid in excess of the usual 3 to 5 mg. per kg. per day from the time of initiation of isoniazid treatment has the clinical incidence of emergence of such catalase-positive mutants so far been markedly reduced (7).

The case reported here was initiated and maintained on 5 mg. of isoniazid per kg. per day until signs of meningitis appeared, at which time the dose was doubled. It seems possible that, had this patient been initiated and maintained on a higher dosage of isoniazid, along with the pyridoxine which appears to prevent peripheral neuropathy (8–10), meningitis might not have occurred.

SUMMARY

The clinical course and pathologic and microbiologic findings in a case of tuberculous meningitis, first appearing and progressing to death under treatment with isoniazid and

streptomycin, are presented. The probable cause and possible prevention of this previously undescribed experience are discussed.

SUMARIO

Meningitis Tuberculosa Letal Aparecida Durante la Isoniacido-Estreptomicina-Terapia

Describense la evolución clínica y los hallazgos histopatológicos y microbiológicos en un caso de meningitis tuberculosa, que apareció y avanzó hasta la muerte bajo tratamiento con isoniacida y estreptomicina. Discútense la probable causa y posible prevención de este acontecimiento que no había sido descrito antes.

RESUME

Méningite tuberculeuse fatale survenue pendant l'isoniazide-streptomycinothérapie

Le cours clinique et les résultats des examens microbiologiques et histo-anatomo-pathologiques d'un cas de méningite tuberculeuse, dont l'apparition initiale et l'évolution fatale se sont produites au cours d'un traitement par l'isoniazide et la streptomycine, sont exposés. La cause probable et la prévention de cette manifestation non encore décrite sont commentées.

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PERSISTENT FIBRIN BODIES PRESENTING AS COIN LESIONS[1]

JOHN R. BUMGARNER, MAX GAHWYLER, AND D. E. WARD

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INTRODUCTION

Fibrin bodies are considered to be concretions of fibrin which occur in the presence of fluid (1). There is general agreement that the presence of an effusion is necessary for the formation of a fibrin body; these bodies appear especially during the stages of beginning resolution and organization of the exudate. Their development depends on a fluid very rich in fibrin (2). The presence of an effusion usually has been noted for some time prior to the appearance of the fibrin bodies. Zavod felt that most of the fibrin bodies disappeared spontaneously and were of no clinical importance (3). He noted an incidence of five cases of fibrin bodies among 226 patients who received artificial pneumothorax. Robins and others observed an incidence of 21 per cent among 75 patients who received artificial pneumothorax (2). Fibrin bodies are usually periform or spherical and are located near the diaphragm. They are usually single. They may remain for long periods of time, may degenerate, may organize or disappear (1).

Before resection became such an important part of the over-all therapy of pulmonary tuberculosis, fibrin bodies were of only academic interest. They produced no symptoms and no complications. Since resection has been used more and more in tuberculosis treatment, however, the differential diagnosis of localized circumscribed lesions has received a great deal of attention. Persistent fibrin bodies give a roentgenographic appearance similar to any other coin lesion and their presence should be excluded before a resection is performed. A history of a therapeutic pneumothorax with effusion and a series of films showing the progressive development of the rounded lesion would be useful in establishing its identity.

In the case described in the present report, the films showed, first, the pneumothorax; then, the development of effusion; and, finally, the gradual development of persistent fibrin body. The fibrin body persisted after the pneumothorax was re-expanded and could easily have been mistaken for a parenchymal "coin" lesion.

CASE REPORT

A 27-year-old white female was well until an influenza-like attack in January, 1941, which was followed by a period of general malaise, productive cough, and weight loss. She consulted her local physician for these symptoms in April, 1941, and her condition was first diagnosed as a case of chronic malaria. In May, 1941, however, she was seen at the outpatient clinic of the North Carolina Sanatorium at McCain, North Carolina, and at this time a chest roentgenogram revealed extensive bilateral pulmonary tuberculosis. The patient's sputum was found to be positive for tubercle bacilli. She stayed in bed at home until August 9, 1941, when she was admitted to the North Carolina Sanatorium at McCain. Bilateral pneumothorax was induced successfully within the first three months of hospitalization, giving a satisfactory collapse on each side. Tubercle bacilli had disappeared from the sputum by February, 1942, but the patient was kept on bed rest due to continuous moderate elevation of temperature for the first year.

The patient was kept in the sanatorium until 1946, when she was discharged and continued to work as an employee at the sanatorium until November, 1947, when it was recommended that her pneumothorax be re-expanded. At the time of discontinuation of the

[1] From Western North Carolina Sanatorium, Black Mountain, North Carolina.

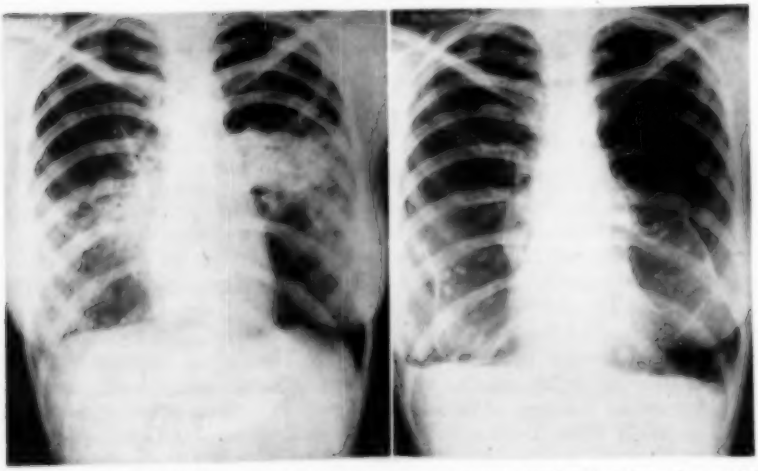

FIG. 1 (Left). Admission film obtained on August 11, 1941, showing far advanced bilateral pulmonary tuberculosis.

FIG. 2 (Right). Film dated September 28, 1945, showing bilateral satisfactory pneumothorax with a moderate amount of fluid in both costophrenic angles.

FIG. 3. Film dated October 16, 1947, showing the formation of a large fibrin body in the right lower pneumothorax space with a moderate fluid level in the costophrenic angle. The left side is also under expansion.

pneumothorax the patient formed a considerable amount of fluid on the right side. The pleural space was aspirated for several weeks and large quantities of fluid were removed at each thoracentesis. However, both lungs were gradually re-expanded over a period of approximately ten weeks.

FIG. 4. Film dated July 7, 1954, showing a fibrin body fixed to the posterior chest wall above the costophrenic angle.

In 1946 and 1947, just prior to and during the time of re-expansion of her pneumothorax on the right side, a large fibrin body measuring about 6 to 7 cm. in its greatest diameter developed on the right in the posterior costophrenic angle. This was well visualized on the roentgenogram, and the appearance of this large fibrin body did not change during the time of re-expansion.

In the following years the patient worked as a nurse's aide at the Western North Carolina Sanatorium, Black Mountain, North Carolina, and was apparently in good health. She had a therapeutic abortion performed in December, 1949, without any reactivation of her tuberculosis.

In February, 1952, the patient had the first reactivation of the tuberculosis in the right upper lobe and her sputum was found to be positive for acid-fast bacilli on microscopy. She was admitted to the Western North Carolina Sanatorium and was started on streptomycin-PAS therapy on March 5, 1952. This was continued until April 10, 1953. The reactivation on the right side cleared rapidly, tubercle bacilli disappeared from the sputum and remained absent during the time of her hospitalization. Despite the other roentgenographic changes, there were no changes in the large fibrin body in her right lower chest. In April, 1953, the patient was discharged as having arrested pulmonary tuberculosis. She continued to do well clinically until June, 1953, when a new extension of her disease in the right upper lobe was discovered. The sputum was again positive for acid-fast bacilli on microscopy. The patient felt well, however; she had no weight loss, cough, or other constitutional symptoms. She was admitted for the second time to the Western North Carolina Sanatorium. Isoniazid-PAS therapy was started and continued throughout her stay until September 9, 1954. The sputum became negative for tubercle bacilli two months after institution of her treatment. A bronchoscopy performed in June, 1953, revealed no endobronchial disease. During her hospitalization the extension of her disease on the right cleared gradually and the patient was again discharged on September 24, 1954, with ar-

rested pulmonary tuberculosis. Surgery was not considered because of the extensive bilateral disease.

During the past eight years, the large fibrin body in the patient's posterolateral sinus did not show any roentgenographic change and is still well visualized on regular posteroanterior and lateral films. Without the history and the serial roentgenograms, it is believed that this fibrin body could very easily be mistaken for a parenchymal lesion which required resection.

SUMMARY

A case is presented of a patient who developed a large fibrin body in her right pleural space during pneumothorax. This fibrin body persisted after re-expansion of the pneumothorax and now presents as a well circumscribed "coin lesion." It is believed that this type of lesion might be considered in the differential diagnosis of a coin lesion, especially in patients who have had a previous pleural effusion.

SUMARIO

Cuerpos Persistentes de Fibrina Semejando Lesiones Redondas

Preséntase el caso de una enferma que manifestó un cuerpo grande de fibrina en el espacio pleural derecho durante el neumotórax. Este cuerpo fibrinoso persistió después de la reinsuflación del neumotórax y tiene aspecto ahora de una "lesión redonda" bien circunscrita. Parece que vale la pena considerar esta forma de lesión en el diagnóstico diferencial de una lesión redonda, sobre todo en casos en que ha habido antes derrame pleural.

RESUME

Corps fibrineux persistants ayant l'aspect de lésions numnulaires

Présentation d'une observation de malade chez laquelle une large masse s'est développée dans l'espace pleural droit au cours d'un pneumothorax. Ce corps fibrineux persistait après la réexpansion du pneumothorax et se présente maintenant sous l'aspect d'une lésion numnulaire bien circonscrite. L'auteur a l'impression que ce type de lésion pourrait être pris en considération dans le diagnostic différentiel d'une lésion numnulaire, surtout dans les cas ayant présenté un épanchement pleural.

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LEAK OF AIR FROM PNEUMOPERITONEUM PRODUCING LEFT-SIDED PNEUMOTHORAX[1]

RICHARD H. LINN,[2] JOHN J. WALSH, AND WILLIAM H. SAGE, III

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INTRODUCTION

Since the entity of spontaneous pneumothorax complicating pneumoperitoneum treatment was first described by Mellies in 1939 (1), the condition has become well known, twenty-five cases having been reported (1–12, 16, 17).

While there is no unequivocal explanation for the preponderance of left-sided pneumothorax as a complication of pneumoperitoneum, one explanation frequently given concerns small congenital defects in the diaphragm and the protective role of the liver in its normal position.

Small defective areas in the diaphragm are generally undiscovered when they lie on the right side, for they are protected by the apposition of the liver to the inferior surface of the diaphragm. The same type of areas in the left hemidiaphragm will be subjected from birth to normal alterations in the intra-abdominal pressure. Thus, they may eventually enlarge to produce detectable hernias or, due to the constant stimulus provided, may gradually contract by scar formation. When a pneumoperitoneum is introduced, the liver is separated from the diaphragm, thus exposing any potentially weakened areas (including the bare area) to the varying abdominal pressures which are raised by the procedure to more than normal limits. It is conceivable that these areas, now unsplinted by the liver and without the relative immunity to stress conferred on those of the left side by a lifetime of meeting the changing abdominal pressures, may gradually weaken and rupture, allowing air to pass the diaphragmatic barrier. Mechanisms other than the one outlined have also been proposed. For a fuller discussion of these, the reader is referred to the articles listed in the references (6, 9, 13, 14).

There is general agreement in the literature that most cases of pneumothorax arising as a complication of pneumoperitoneum involve the right side; indeed one reads repeatedly such statements as "The cases of pneumothorax complicating pneumoperitoneum reported in the literature have all been right-sided" (11). The following case is presented because it is one of the few cases involving the complication of left-sided pneumothorax which may be found in the literature. In fact, only one article refers to this entity; Ross and Farber (6) report twenty-three cases of spontaneous pneumothorax complicating pneumoperitoneum, of which all but one were right-sided. The left-sided one was reported to them in answer to a questionnaire and was not associated with loss of air from the peritoneal cavity. One case of fatal bilateral pneumothorax is reported (15). A review of the subject (9) erroneously cites the case reported by Banyai and Jurgens (2) as being left-sided; it was, in fact, right-sided.

CASE REPORT

Tuberculosis was first discovered in the patient in the present case in March, 1948. At that time a chest roentgenogram showed extensive, bilateral exudative lesions. He was hospitalized for approximately one year at the U. S. Public Health Service Hospital, Seat-

[1] From the Medical Service, U. S. Public Health Service Hospital, Seattle, Washington.

[2] Present address: Medical Service, U. S. Public Health Service Hospital, New Orleans, Louisiana.

tle, Washington. Thereafter he was followed as an outpatient until he complained of a slight increase in cough. At this time studies revealed the presence of acid-fast bacilli in the sputum, and he was readmitted to the hospital in January, 1950. His films at this time were thought to show fibrocalcific disease, and no evidence of bullae was demonstrated then or later.

The patient was placed on bed rest and antimicrobial therapy but failed to make good progress, so pneumoperitoneum was added on October 25, 1950. He tolerated the latter therapy well, although a laxness of the abdominal wall forced him to wear an abdominal binder most of the time. He was discharged from the hospital on June 9, 1953, and the pneumoperitoneum was maintained on an outpatient basis. The refills averaged 900 cc. per week, with average pressures of plus 10 to plus 13.

Two hours following the refill of June 25, 1953, which was made as usual one inch inferior and two inches to the left of the umbilicus, he suddenly developed dyspnea and persistent cough. On July 2, 1953, he reported to the clinic, at which time he was fluoroscoped by two observers, and a fairly large pneumothorax was detected on the left. There was no evidence of mediastinal emphysema by either roentgenographic or physical examination. Five hundred cubic centimeters of air were withdrawn from the peritoneal cavity with immediate and striking relief of symptoms of cough and dyspnea. Fluoroscopy by the same observers showed the pneumothorax to be slightly decreased in size and no appreciable change in the position of the diaphragm (figure 1). On July 11, pneumothorax was still present but was greatly diminished. On July 23, only slight pneumothorax remained (figure 2), and his pneumoperitoneum was supplemented with 500 cc. of air without incident. He was given regular refills of similar amounts of air until the pneumoperitoneum was discontinued in January, 1954, and no subsequent pneumothorax was ever detected. The extent of pneumoperitoneum was never allowed to approach that existing prior to the episode of pneumothorax, as judged by clinical, fluoroscopic, and manometric standards.

FIG. 1. Roentgenogram obtained July 2, 1953, revealing left pneumothorax

FIG. 2. Roentgenogram obtained July 23, 1953, revealing only minimal pneumothorax and reduced pneumoperitoneum.

COMMENT

Right-sided pneumothorax complicating pneumoperitoneum therapy is not rare. Left-sided pneumothorax, however, with or without loss of air from the peritoneal cavity, has been reported only once (6), and in this case there was no associated loss of air from the peritoneal cavity.

While it is recognized that it cannot be proved conclusively that the case reported above was not a case of ordinary spontaneous pneumothorax occurring in a patient who was concurrently receiving pneumoperitoneum, it is believed that air did pass from the peritoneal cavity into the left pleural space, even though there was no demonstrable decrease in the size of the pneumoperitoneum space. This is best demonstrated by the fact that withdrawal of 500 cc. of air from the peritoneal cavity produced a decrease in the size of the pneumothorax space which was verified at fluoroscopy by two observers. This withdrawal of air from the peritoneal cavity was likewise associated with an abrupt cessation of the symptoms of dyspnea and cough which had persisted since the onset of the condition. Furthermore, this cessation of dyspnea could not have been due to the relaxation of the diaphragm since no appreciable fluoroscopic change in its position could be detected following the withdrawal of the air. More air would probably have entered the left pleural space with concomitantly greater collapse of the left lung had it not been for the extensive pleural symphysis present in the apical area.

SUMMARY

A case of left-sided pneumothorax due to the passage of air from a pneumoperitoneum into the left pleural space is reported.

Following the absorption of air from the pleural space, the pneumoperitoneum was continued for an additional seven months without incident.

SUMARIO

Escape de Aire del Neumoperitoneo Produciendo Neumotórax Levolateral; Primer Caso Comunicado

Preséntase un caso de neumotórax del lado izquierdo, debido al paso de aire procedente de un neumoperitoneo al espacio pleural izquierdo.

Después de la adsorción del aire del espacio pleural, se continuó el neumoperitoneo otros siete meses sin incidente alguno.

RESUME

Fuite d'air provenant d'un pneumopéritoine provoquant un pneumothorax gauche; Premier cas rapporté

Un cas de pneumothorax gauche par passage de l'air d'un pneumopéritoine dans la cavité pleurale gauche est rapporté.

Après adsorption de l'air de la cavité pleurale, le pneumopéritoine fut poursuivi sans incident pendant les sept mois suivants.

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COEXISTENT PULMONARY TUBERCULOSIS AND FUNGAL DISEASE[1]

A Review of the Literature and Three Additional Cases

JOHN C. LARKIN, JR., AND SAMUEL PHILLIPS

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INTRODUCTION

The high incidence of pulmonary tuberculosis, and the greater ease with which fungal disease may now be diagnosed, lead one to expect that the coexistence of tuberculosis and fungal disease would be frequently reported. Except for the combination of tuberculosis and coccidioidomycosis, however, the coexistence of pulmonary tuberculosis and a fungal infection has been reported infrequently. More cases of dual infection presumably occur, but are overlooked because repeated examinations of the sputum for fungi are not usually a routine procedure in patients with pulmonary tuberculosis. The importance of coexistent pulmonary tuberculosis and fungal disease was impressed upon the writers by experiences with 3 cases of combined infections of the lung which were treated on the pulmonary disease section of Kennedy Veterans Hospital. The outstanding feature was the unfavorable course pursued by the double infection in all 3 patients.

Very little information is available on the beneficial or adverse effects of therapy on one infection when directed against the other infection.

Review of Literature

Greer and Gemoets (1) reported their findings on 301 patients consecutively admitted to the Houston Tuberculosis Hospital, of whom 295 were definitely tuberculous. Fungi were isolated by tracheal aspiration of 12 of the patients; the fungi caused pathologic changes when injected into rabbits. *Cryptococcus hominis*, *Monilia bronchiales*, *Saccharomyces hominis*, *Aspergillus fumigatus*, *Sterigmatocytis nidulans*, and *Sporotrichum schenckii* were isolated. These writers found that in the great majority of their cases of double infection the pulmonary tuberculosis had progressed to a far advanced stage in an average of 9.6 months since the onset of clinical symptoms. This led them to suggest "that the association of a fungus infection of the lung in a patient having pulmonary tuberculosis would augment and accelerate the activity of the tubercle bacilli, either directly or by lowering the vitality and resistance of the patient to the end that a more unfavorable course of the tuberculous disease marked by relapses and relatively rapid progression may be observed."

Stein (2) studied fifteen cases of coexisting pulmonary tuberculosis and coccidioidomycosis encountered at the Tucson Veterans Administration Hospital. He discusses the question whether tissue with coccidioidal infection is more susceptible to invasion by tubercle bacilli. He states that, because relatively few of the many cases of coccidioidomycosis which occur in endemic areas subsequently develop tuberculosis, it must be concluded that coccidioidal infection apparently does not predispose to tuberculous infection. Stein's experience with the dual infection has led him to believe that it is no more severe than that caused by either parasite alone. He cites six cases in some detail, including one of a patient who died of disseminated coccidioidomycosis while the tuberculous lesions seem-

[1] From the Pulmonary Disease Section, Medical Service of the Veterans Administration Medical Teaching Group (Kennedy) Hospital, Memphis, Tennessee.

ingly improved. In the five other cases, the lesions produced by both infections improved. Cotton and associates (3) treated twenty-four patients who had coexisting pulmonary coccidioidomycosis and tuberculosis. Nine of the cases were successfully treated by resectional surgery. Fifteen patients were treated nonsurgically, of whom ten were under active therapy, and five under outpatient supervision at the time of writing. Greer and Grow (4) treated ten patients with coccidioidomycosis by surgical procedures; one of these patients also had tuberculosis. After the operation, this patient developed hemoptysis and was found to have a small cavity in the remaining portion of the operated lung with sputum positive for acid-fast tubercle bacilli. There was no statement as to his further course. Kahn (5) reported a case with both pulmonary tuberculosis and coccidioidomycosis which showed satisfactory healing of both pulmonary infections. A patient with coccidioidomycosis who developed pulmonary tuberculosis was described by Study and Morgenstern (6). No therapy could be instituted because the patient left the hospital prematurely and no follow-up of his course was available. Smith and associates (7) studied the records of 274 cases of coccidioidomycosis with cavitation and found coexisting tuberculous infections in seven cases. In only one was the tuberculosis progressive. The therapy given prior to diagnosis of tuberculosis was not reported. Firestone and Benson (8) reported a case of coccidioidomycosis which was treated with potassium iodide with initial improvement. The patient later developed increased disease, due to coccidioidomycosis and tuberculosis, while receiving the potassium iodide therapy. At autopsy there was evidence of disseminated coccidioidomycosis, and tuberculosis of the lungs, pharynx, and bowel, as well as a hematogenous dissemination to the seminal vesicles. Streptomycin had been of value in controlling the tuberculous infection of the pharynx and tonsils. Hyde and Hyde (9) discussed a patient who had disseminated coccidioidomycosis and disseminated lymphohematogenous miliary tuberculosis. Both the fungus and the tubercle bacillus were found in many different tissues. The authors state that "one might postulate that coccidioidal nodules in addition to suppuration may have activated an old tuberculous focus, so that both the tubercle bacilli and the *Coccidioides* were later disseminated from approximately the same site. . . . Another possibility is that the patient acquired coccidioidomycosis and the primary infection with tuberculosis at about the same time."

In a discussion of histoplasmosis by Parsons and Zarafonetis (10), among seven cases which are cited in some detail, there is one patient who was treated for active pulmonary tuberculosis for approximately seven weeks, but who was found, at autopsy, also to have had histoplasmosis. There is no report of the therapy instituted or the possibility of its aggravation of either condition. Charr (11) reported two cases of death due to histoplasmosis, but one patient showed coexisting pulmonary tuberculosis. During the latter's illness, cavitation developed in the infiltrate and tubercle bacilli were found in the bronchial secretions. There was no evidence, however, of spreading pulmonary involvement with tuberculosis. Meleney (12) described two cases of histoplasmosis, both of which were complicated by pulmonary tuberculosis. In one case, at autopsy, in addition to the lesions of histoplasmosis, there were small caseous areas in the lung, liver, and spleen which showed acid-fast bacilli. The author believed that the presence of calcified areas in the lungs was indicative of a previous tuberculous infection. The lowered resistance of the patient was thought responsible for both the reactivation of a silent tuberculous infection and the development of histoplasmosis from parasites already present in the respiratory tract. In the second case, there was a roentgenographic picture consistent with pulmonary tuberculosis, and acid-fast bacilli were found in the sputum on two occasions. At autopsy there was no evidence of widespread tuberculosis, but evidence which suggested that histoplasmosis was responsible for the terminal pulmonary lesions was pres-

ent. Rodger and co-workers (13) cite a case of Hodgkin's disease complicated by histoplasmosis, cryptococcosis, and tuberculosis. The *Cryptococci* had been seen on a biopsy specimen of a cutaneous lesion but no culture was made of the biopsied material. At autopsy no *Cryptococci* were found, but both tubercle bacilli and *Histoplasma capsulatum* were widely distributed

Cryptococcosis and coexisting pulmonary tuberculosis have also been reported. Corpe and Parr (14) treated a young man for moderately advanced pulmonary tuberculosis with streptomycin and para-aminosalicylic acid. He seemed to respond with progressive improvement, although a round solitary lesion remained. When this area excavated, it was removed, and *Cryptococci*, but no acid-fast tubercle bacilli, were found in the resected specimen. Voyles and Beck (15) reported four patients with systemic cryptococcosis among whom there was one patient with advanced silicotuberculosis whose sputum was positive for tubercle bacilli. This patient was in the hospital for twenty-four days before death and was treated with potassium iodide and sulfadiazine. It is not stated whether this treatment resulted in a clinical worsening of the tuberculous infection but at autopsy the tuberculous infection was confined to the lungs and spleen.

OBSERVATIONS

The 3 patients with dual fungal-tuberculous infections observed by the present writers had histoplasmosis, coccidioidomycosis, and cryptococcosis, respectively, along with tuberculosis. Two of the patients died in the hospital, and the other died at home soon after leaving the hospital. In retrospect, it would seem that 2 of these patients received drug therapy which may have adversely affected the tuberculosis. The 3 cases are reported in detail.

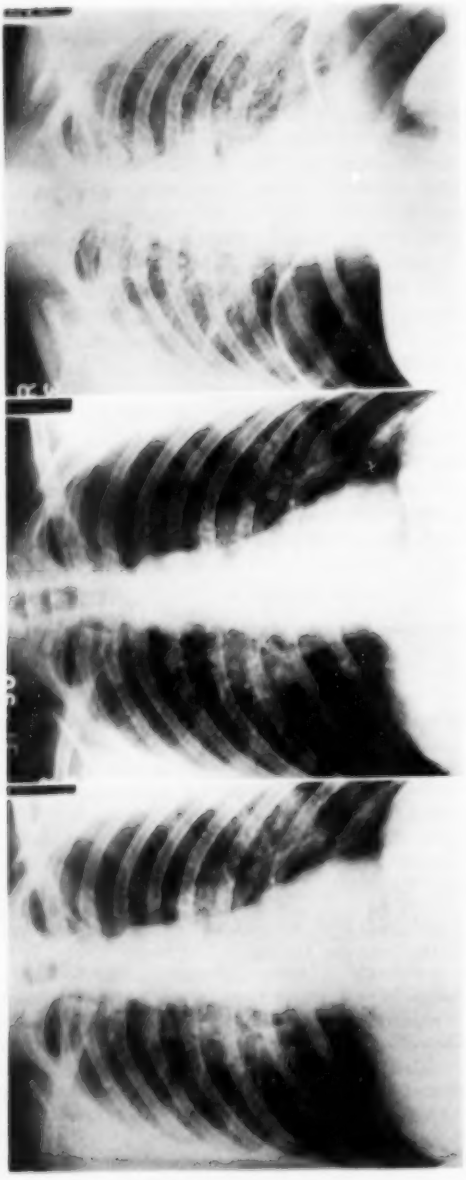
CASE REPORTS

J. E. R., a 37-year-old white male, was admitted to the Kennedy Veterans Hospital on November 7, 1949, after a routine chest roentgenogram had revealed bilateral infiltrations (figure 1). Cultures of sputum and gastric washings were negative for tubercle bacilli and fungi. The tuberculin tests and the skin tests with histoplasmin, coccidioidin, and blastomycin were negative. Because of these negative findings, the patient was discharged under the care of his physician.

Two weeks after discharge, the patient began to notice malaise with fever and night sweats. He was readmitted to the hospital, and the chest roentgenogram showed an additional patchy infiltration at the left base (figure 2). Cultures of the sputum at this time were positive for tubercle bacilli, but negative for fungi. Microscopic examination of the sputum revealed no tumor cells. The patient was treated with pneumoperitoneum and daily streptomycin-PAS. There was no change roentgenographically, but the sputum became negative for tubercle bacilli on culture.

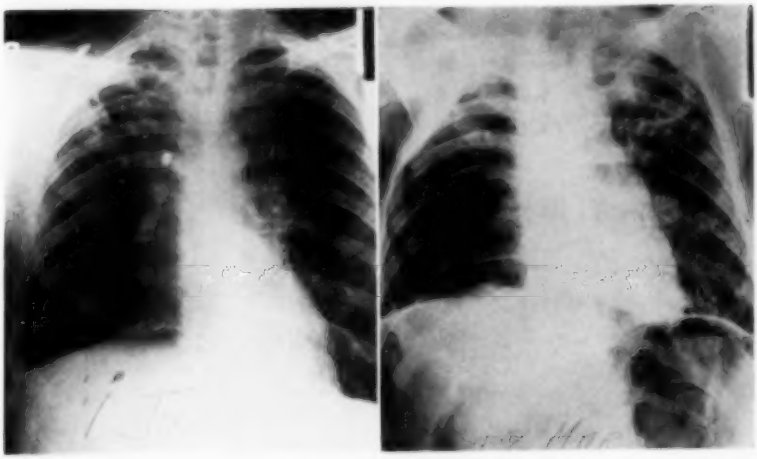
Because the expected roentgenographic clearing failed to appear, it was suspected that another disease might coexist. On December 11, 1950, a lung biopsy was performed and the specimen revealed *Cryptococcus hominis* on microscopic examination and on culture. The patient was transferred to another service, where he was treated with potassium iodide for five months, ethyl vanillate for thirty-four days, and actidione for twenty-one days, without improvement. No antituberculous drugs were used during this time, but the pneumoperitoneum was maintained.

In June, 1951, the patient began to have fever, and the sputum again contained tubercle bacilli, although it remained consistently negative for *Cryptococci*. Treatment with 1 gm. of streptomycin twice daily was reinstituted, but the patient's condition deteriorated rapidly and the chest roentgenogram showed increased disease (figure 3). The patient died on July 30, 1951. An autopsy showed widespread miliary tuberculosis but no evidence of cryptococcosis, even on culture of tissues.



Case 1 (J. E. R.)

FIG. 1 (Left). Chest roentgenogram, taken November 14, 1949 showing bilateral infiltrations.
FIG. 2 (Center). Chest roentgenogram, taken January 31, 1950, showing additional patchy infiltrate at left base.
FIG. 3 (Right). Chest roentgenogram, taken on July 17, 1951, revealing increased disease bilaterally.



Case 2 (C. C. W.)

FIG. 4 (Left). Chest roentgenogram, taken June 7, 1951, showing infiltrate in right upper lung field.

FIG. 5 (Right). Chest roentgenogram, taken March 12, 1953, showing extensive disease in the left lung.

C. C. W., a 46-year-old white male, was found to have pulmonary tuberculosis in 1947, and had been treated by bed rest in a local sanatorium since 1948. In 1950, a right phrenic crush was performed and he was discharged in April, 1951. At home, he continued to notice a chronic cough with intermittent blood streaking and fever. He was admitted to another Veterans Administration hospital, where the chest roentgenogram showed an infiltrate in the right upper lung field (figure 4). The sputum was negative on culture for tubercle bacilli. The patient was transferred to the thoracic surgery section of Kennedy Veterans Hospital, where it was considered that he probably had a residual bronchiectasis.

On August 3, 1951, a right upper lobectomy was performed, followed two weeks later by a postresection thoracoplasty. Streptomycin and PAS were given for a period of three weeks in association with the operations. *Histoplasma capsulatum* was cultured from the resected specimen, but no tubercle bacilli were found. The patient was then transferred to a medical section where, two months after surgery, an infiltration was discovered in the left apex. Therapy was started with streptomycin and a three-weeks' course of ethyl vanillate. The sputum was reported positive on culture for tubercle bacilli, and the patient was transferred to the pulmonary disease section. He was treated at first with streptomycin-PAS, and later with viomycin and isoniazid, but the patient's strain of tubercle bacilli became resistant to all of these drugs. The sputum remained negative for *Histoplasma capsulatum*. A pneumoperitoneum was instituted in February, 1953, and was continued during the remainder of the patient's stay in the hospital. His course was one of progressive deterioration. His sputum was intermittently streaked with blood and there was increasing disease on repeated roentgenographic examinations (figure 5). The sputum remained negative for *Histoplasma* but continued to be positive for tubercle bacilli. After a suicidal attempt, the patient was to be transferred to a neuropsychiatric hospital, but he refused, and left the hospital against medical advice on July 11, 1953. He died at home soon afterwards.

Case 3 (C. H. D.)

FIG. 6 (Left). Chest roentgenogram, taken February 26, 1952, showing the pneumothorax on the right and the density in the left extending from the base to the apex.

FIG. 7 (Right). Chest roentgenogram, taken May 4, 1953, revealing the empyema on the left and increased disease in the right lung.

A 30-year-old white male, C. H. D., was admitted to the Kennedy Veterans Hospital on February 25, 1952, complaining of fever, increased productive cough, and weight loss. In 1944, he was discharged from the service with the diagnosis of coccidioidomycosis. Several months later he was told that he had tuberculosis and was hospitalized for eighteen months. At this time he received bilateral pneumothoraces and pneumolyses in addition to eight-weeks' therapy with streptomycin. The right pneumothorax was continued until the present hospitalization, but the left pneumothorax had been abandoned.

On examination at this hospital, the patient was chronically ill, with a temperature of 99.6°F. The abnormal findings were limited to the chest, with signs of pneumothorax on the right and dullness with absent breath sounds at the left apex. The sputum was positive for tubercle bacilli. The chest roentgenogram revealed a deviation of the mediastinum to the left, and elevation of the left diaphragm and contraction of the left thoracic cage. There was a dense homogenous shadow overlying the apex of the left lung which extended along the periphery of the chest cage to the base and was considered to be due to fluid or thickened pleura. On the right there was a pneumothorax with 50 per cent collapse of the lung. Scattered areas of infiltration and an area of radiolucency were present in the right lung (figure 6). Therapy with streptomycin-PAS was instituted.

Attempts to aspirate fluid from the left chest were complicated by the development of a bronchopleural fistula and an empyema which failed to respond to repeated aspirations and a closed thoracotomy. The pneumothorax on the right was permitted to re-expand gradually. To obtain better drainage of the empyema, a resection of the eighth rib posteriorly was performed on August 29, 1952. Isoniazid (300 mg. daily) was added to the antituberculous therapy.

On October 3, 1952, resection of the posterior apical segment of the left upper lobe and a

left decortication were performed. Microscopy and cultures of the resected tissue showed *Coccidioides immitis* and *M. tuberculosis*. The sputum had been negative for tubercle bacilli for two months prior to surgery and both the sputum and empyema fluid remained negative after the operation.

In May, 1953, *Coccidioides immitis* was isolated from the empyema fluid, but was not isolated from the sputum. The chest roentgenogram showed an increase in the disease in the right upper lung field in January, 1953, and continued to show increasing disease until the patient's death (figure 7). It was considered that this progressing lesion was probably due to tuberculosis although the sputum remained negative for tubercle bacilli. The bronchopleural fistula remained open and the patient developed hypertrophic pulmonary osteoarthropathy. Following the onset of recurring hemoptyses, the patient died on July 2, 1953. No autopsy was obtained.

COMMENT

The 3 cases of dual fungal-tuberculous infection described above all had a fatal termination. There was known progression of tuberculosis in 2 cases, and the progressive disease in the third instance was presumed to be due to tuberculosis. The poor outcome in these patients may have been due to a lowering of the body resistance to tuberculosis as a result of the double infection, or perhaps as a result of the therapy directed against the fungal infection. In the first case (tuberculosis and cryptococcosis), the sputum had become negative for acid-fast bacilli before potassium iodide was used. This treatment was followed by the re-appearance of tubercle bacilli in the sputum, and the patient developed miliary tuberculosis. It has long been taught that iodides are contraindicated in the presence of tuberculosis unless as a "provocative" test. A study in the Nashville Veterans Administration Hospital, however, has shown that iodides used along with specific antituberculous drugs have no deleterious effect on tuberculosis (16). If this patient had continued to receive antituberculous therapy along with the therapy directed against the fungal disease, it is possible that the spread of the tuberculosis might not have occurred.

The second patient, who had arrested tuberculosis, developed histoplasmosis, for which the pulmonary resection was performed. He subsequently received ethyl vanillate which, used in large doses, caused considerable anorexia, nausea, and vomiting. These symptoms, with the lowering of general resistance, may have been responsible to a large degree for the reactivation of the tuberculosis, which progressed in spite of antimicrobial therapy.

The third patient, who had coccidioidomycosis and later developed tuberculosis, which became complicated by a bronchopleural fistula and empyema, developed increasing disease in the opposite lung. Culture of the empyema fluid revealed *Coccidioides immitis* on one occasion but tubercle bacilli could not be cultured from this fluid. It may have been that the development of the bronchopleural fistula, attributed to the cryptococcosis, caused a lowering of the general body resistance which led to increased disease in the opposite lung, presumably due to tuberculosis, in spite of the antituberculous therapy.

SUMMARY

Double infection of the lung with tuberculosis and a fungal disease appears to have a poor prognosis. This may be due to lowered host resistance, or possibly to the therapy directed against the fungal infection which may exert a deleterious influence upon the coexistent tuberculosis. Unless an agent is known to have a specific beneficial effect upon a particular fungal disease, such as stilbamidine in blastomycosis, any possible ill effect upon the tuberculosis should be very seriously considered before the agent is employed to treat coexisting fungal infections.

SUMARIO

Coexistencia de Tuberculosis Pulmonar y Micosis: Repaso de la Literatura y Adición de Tres Casos

Las infecciones combinadas de tuberculosis y micosis parecen tener un pronóstico malo. Esto puede deberse a disminución de la resistencia o posiblemente a la terapéutica asestada a la fungosis, que puede ejercer efecto nocivo sobre la tuberculosis coexistente. A menos que se conozca un agente dotado de efecto beneficioso específico sobre la micosis, tal como la estilbamidina en la blastomicosis, hay que considerar seriamente todo posible efecto adverso sobre la tuberculosis, antes de emplear el agente para tratar la infección coexistente.

RESUME

Coexistence de tuberculose et de mycose pulmonaires: Un compte-rendu de la littérature et trois cas additionnels

L'association de la tuberculose et d'une mycose au niveau du poumon apparait d'un mauvais pronostic. Ceci peut être dû à une diminution de la résistance ou, peut être, au traitement dirigé contre l'infection fongique pouvant exercer une influence nocive sur la tuberculose coexistante. A moins de disposer d'un agent reconnu apte à exercer une action spécifique favorable sur la mycose, tel que la stilbamidine dans la blastomycose, tout effet nocif sur la tuberculose doit être sérieusement pris en considération avant d'utiliser cet agent pour traiter l'infection coexistante.

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ADDISON'S DISEASE ASSOCIATED WITH DISSEMINATED HISTOPLASMOSIS AND PULMONARY TUBERCULOSIS[1]

MARTIN J. FITZPATRICK AND MELVIN D. REUBER

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The combination of active pulmonary tuberculosis and disseminated histoplasmosis in a patient with adrenal insufficiency is infrequent. It is rare for both coexistent diseases to be diagnosed during life, and to have the opportunity to observe the effects of therapy on both the mycobacterial and fungal infections. Recent experience with a patient presenting the picture of classical Addison's disease secondary to disseminated histoplasmosis, with coexistent active pulmonary tuberculosis, has prompted the report of this interesting problem.

CASE REPORT

The patient, E. A., a 49-year-old white male oil driller, was admitted to the University of Kansas Medical Center in February, 1954, complaining of abdominal pain, fever, and weight loss. He had been well until April, 1953, when the onset of right lower quadrant abdominal pain was first noted. Initially, this dull, nonradiating pain appeared fifteen to thirty minutes after meals and lasted for approximately one-half hour. Other gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, were denied. During the following eight months the pain became more severe and constant, and involved both upper abdominal quadrants. In this interval, a weight loss from 112 to 105 pounds was noted.

In September, 1953, the patient noted the onset of slight exertional dyspnea and an infrequent dry cough. The latter gradually increased in frequency and was productive of small amounts of tenacious sputum. This was accompanied by progressive weakness, malaise, nocturnal fever, diaphoresis, and occasional shaking chills. In November, 1953, the patient discontinued work because of the above symptoms.

In December, 1953, he was admitted to the Kansas State Tuberculosis Sanatorium with a presumptive diagnosis of active pulmonary tuberculosis. The patient's wife was known to have had moderately advanced tuberculosis with sputum repeatedly positive for tubercle bacilli by culture since February, 1952. Three of four children, ranging in age from two to twelve years, had skin tests positive to both tuberculin (PPD) and histoplasmin

Chest roentgenograms shortly after admission revealed a fibrotic appearing infiltration with possible cavitation in the right upper lobe of the lung. Body section roentgenograms (figure 1) later confirmed the presence of a 2 cm. cavity in the right upper lobe. Repeated sputum specimens were reported negative on direct smear for acid-fast bacilli. However, the presumptive diagnosis of active pulmonary tuberculosis was made and the patient was started on intermittent parenteral streptomycin, 1 gm. twice weekly, and isoniazid, 300 mg. daily by mouth. Serial roentgenograms of the chest remained unchanged during the next six weeks, during which time the patient failed to show the expected amelioration of symptoms. Because of this, he was transferred to the University of Kansas Medical Center for further study.

Physical examination on arrival at this hospital revealed an emaciated, chronically ill white male, appearing older than his stated age. Increased pigmentation of the skin in general, and numerous small dark nevi over the chest were noted. The blood pressure was 90 systolic, 70 diastolic in mm. of mercury; pulse, 108 per minute, and respirations, 24 per minute. Positive physical findings included a firm, nonfixed, 2 cm. right anterior cervical

[1] From the Department of Medicine, Section for Pulmonary Disease, University of Kansas Medical Center, Kansas City, Kansas.

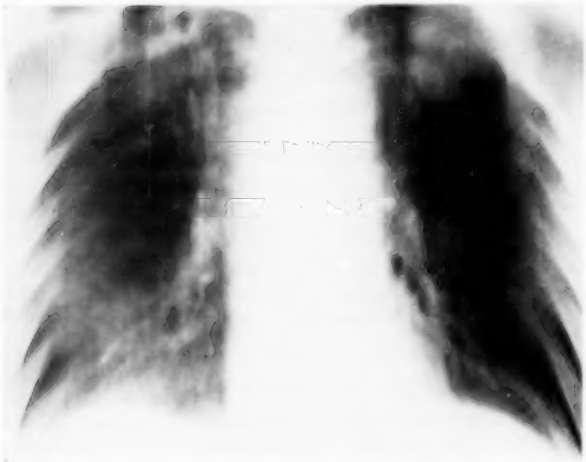

FIG. 1. Tomogram, December, 1953, showing 2.0 cm. cavity in right upper lobe

lymph node. In addition, smaller axillary and inguinal lymph nodes were also noted. Examination of the thorax disclosed diminished breath sounds over the right apex and scattered post-tussive rales in that area. The liver edge extended 4 cm. below the right costal margin. The spleen was not palpable. The remainder of the examination was unremarkable.

Laboratory data on admission disclosed an erythrocyte count of 5,640,000; hemoglobin, 15.8 gm. per 100 ml.; and a leukocyte count of 7,950 per cu. mm. Differential count showed 79 per cent segmented neutrophils, 15 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils. The eosinophilic count was 116 per cu. mm., and the platelet count, 144,000 per cu. mm. Urinalysis revealed a specific gravity of 1.013, albumin which was 2 plus, and sugar which was negative; on microscopy, numerous granular casts and pus cells were seen. The phenolsulfonphthalein excretion was 16 per cent in one hour. A serologic test for syphilis was negative. Sedimentation rate (Cutler) was 20 mm. in one hour. Chemical determinations of the blood revealed results as follows: nonprotein nitrogen, 42 mg. per 100 ml.; creatinine, 2 mg. per 100 ml.; sugar, 72 mg. per 100 ml.; sodium, 122 mEq per L.; potassium, 4 mEq per L.; chloride, 88 mEq per L.; carbon dioxide combining power, 17.5 mEq per L. The total serum bilirubin was 0.5 mg. per 100 ml., and alkaline phosphatase, 4.6 Bodansky units. The cephalin-cholesterol flocculation test gave the result of 4 plus in forty-eight hours. Thymol turbidity was 28 units; serum albumin, 3 gm. per 100 ml.; serum globulin, 3.5 gm. per 100 ml.; cholesterol, 300 mg. per 100 ml.; cholesterol esters, 60 per cent; and serum iron, 151 γ per 100 ml. Urinary 17 ketosteroids were 2.1 mg. in twenty-four hours, while 11-oxysteroids were 2.5 mg. in twenty-four hours.

During the next three months serologic studies were performed repeatedly, using various antigenic fractions of *H. capsulatum*. Complement-fixation tests were consistently negative for histoplasmosis, but the precipitin reactions remained positive and fixed in a dilution of 1 to 40. Skin tests performed on admission revealed a positive reaction to histoplasmin, with negative responses to tuberculin, blastomycin, and coccidioidin. On March 2 and April 20, 1954, the skin tests were repeated and both the histoplasmin and tuberculin skin tests were then negative. Repeated smears of the sputum failed to demonstrate acid-fast bacilli; repeated roentgenographic studies showed the gastrointestinal tract to be normal.

During the second week of hospitalization, biopsy of the right cervical lymph node was performed. Numerous intracellular yeast-phase parasites, typical of *H. capsulatum*, were

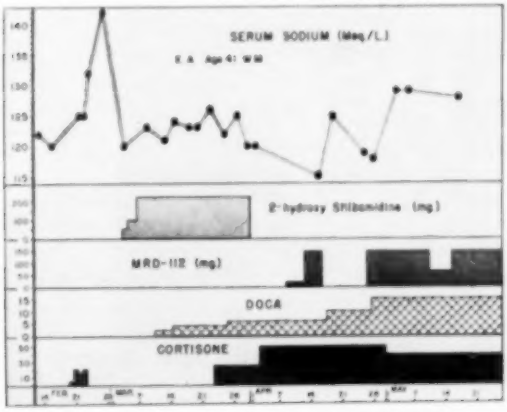

FIG. 2. Effects of therapy on hyponatremia

found on microscopic examination of the fixed and stained lymph node. Cultures of the same node yielded a heavy growth of *Histoplasma*. A bone marrow aspiration was performed and interpreted as being morphologically normal; however, *H. capsulatum* was cultured from the marrow specimen. Needle biopsy of the enlarged liver also yielded *Histoplasma* on culture. The same organisms were cultured from venous blood on two occasions.

The hospital course was one of progressive deterioration during the following three months. The patient presented a most difficult problem of adrenal cortical replacement therapy. Initially, he received 2 mg. of desoxycorticosterone, 25 mg. of cortisone, and 4 gm. of salt by mouth, daily. This was increased gradually to 15 mg. of desoxycorticosterone, 50 mg. of cortisone, and 20 gm. of salt daily (figure 2). Despite these unusually large doses of sodium chloride, and of salt and glucogenic regulating hormones, the patient experienced repeated episodes of acute adrenal crises with prolonged and disturbing periods of medical shock. During the last six weeks of life, he received 500 ml. of 5 per cent sodium chloride by slow intravenous drip daily without developing edema or elevating the serum sodium above 128 mEq per L. This massive electrolyte replacement therapy was required to combat excessive renal loss, particularly of sodium. Daily urinary sodium loss ranged from 200 to 400 mEq per L. The hemoglobin gradually decreased to 9 gm. and the leukocyte count to 2,000 before death. Nitrogen retention did not develop. The liver function studies remained grossly abnormal throughout the hospital course.

On March 4, 1954, the patient was started on 2-hydroxystilbamidine[2] and received 225 mg. dissolved in 250 ml. of 5 per cent glucose in distilled water intravenously for twenty-eight days. Upon completion of this course of therapy a liver biopsy was again performed. Once more, nonspecific granulamatous lesions were visualized and *H. capsulatum* was recovered from culture of the liver biopsy specimen. On April 14, 1954, β-diethylaminoethyl fencholate (MRD-112[3]) was started. After receiving 150 mg. of this drug dissolved in 150 ml. of normal saline by slow intravenous drip for a few days, an episode of acute adrenal insufficiency was experienced and further therapy with β-diethylaminoethyl fencholate was discontinued until April 27. The drug was then resumed in the same dosage, except for a

[2] Generously supplied by Wm. S. Merrell Co., Cincinnati, Ohio, through Dr. M. L. Furcolow, Kansas City, Kansas.

[3] Merrell Research Drug 112, generously supplied by Wm. S. Merrell Co., Cincinnati, Ohio, through Dr. M. L. Furcolow, Kansas City, Kansas.

FIG. 3

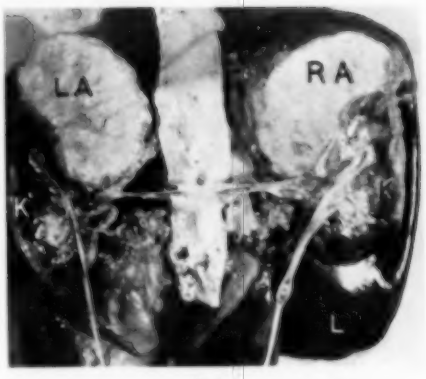

FIG. 4

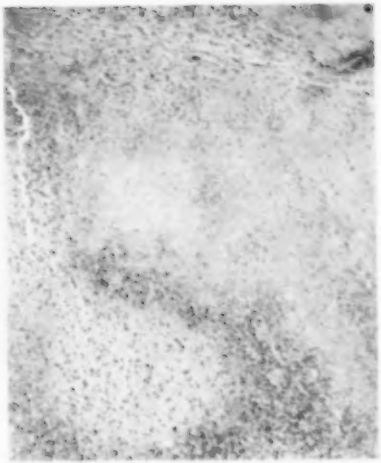

FIG. 5

FIG. 3. Section of lung through cavity wall, showing necrosis, granulation tissue, and giant cells (upper right). (Periodic-acid-Schiff × 100)

FIG. 4. Abdominal organs, posterior view showing relationship of adrenals to other viscera. R. A., right adrenal; L. A., left adrenal; K, kidney; L, liver.

FIG. 5. Section of adrenal gland, showing capsule (top), necrosis of most of cortex (center), and a few intact cells (bottom) containing *H. capsulatum*. (Periodic-acid-Schiff × 100)

period of one week when the daily dose was reduced to 60 mg. by mouth, until the death of the patient (figure 2).

One month before death, acid-fast bacilli were seen on a concentrated sputum smear and typical tubercle bacilli were later cultured from this specimen. At that time, reports were received from the Kansas State Tuberculosis Sanatorium stating that tubercle bacilli had been isolated from sputum cultures in December, 1953. The patient was again given intermittent streptomycin, 1 gm. twice weekly, and isoniazid, 300 mg. daily.

During the last month of life, the patient exhibited a low-grade fever, tachycardia, extreme debility, and complained bitterly of persistent abdominal pain. Anorexia and cachexia gradually became more pronounced and the patient died quietly in May, 1954, three months after admission.

Post-Mortem Examination

Only the pertinent gross and microscopic findings are reported.

The body was that of a markedly emaciated white male, measuring 64 inches in length and weighing an estimated 85 pounds. The skin appeared sallow and scaly, and showed brown pigmentation on the neck, forearms, lower legs, hands, and feet. It was most marked over the palmar surface, the knuckles, forearms, and medial aspect of both legs.

In the apex of the right lung, a cavity was found, measuring 1.0 by 1.4 cm. with a dense fibrous wall. A tortuous, thickened bronchus was seen to approach the cavity but direct communication could not be demonstrated. There were smaller caseous nodules measuring approximately 6 mm. in diameter adjacent to the larger lesion. Microscopic examination of the cavity showed extensive central caseation necrosis and irregular peripheral areas of granulation tissue, which were enclosed by a dense fibrous tissue capsule (figure 3). Thick fibrous bands radiated from the capsule and joined the satellite tubercles. Serial sections failed to demonstrate a bronchocavitary communication. Typical *Histoplasma* was observed within macrophages scattered throughout the granulation tissue about the wall of the cavity. Three acid-fast bacilli were found by appropriate staining in the caseous material within the cavity wall. Emphysematous blebs were noted in both apices, and changes compatible with emphysema were noted in all lobes of the lungs.

The adrenal glands were markedly enlarged, weighing an estimated 100 gm. each and measuring 4.5 by 9.5 cm. (figure 4). They were firmly attached to the kidneys but were separated from them by a fibrous capsule. The right adrenal gland was adherent to both the kidney and the right lobe of the liver. On cut surface, both glands were replaced by yellow-gray caseous necrosis. The line of demarcation between the adrenal and kidney was distinct; the boundary between the adrenal and liver was not always so. In several areas, yellow-gray necrotic adrenal tissue extended anteriorly into the right lobe of the liver and assumed a periportal distribution. The left lobe of the liver was not involved. Microscopy showed the adrenals replaced by central caseous necrosis with granulation tissue about the periphery. There were several islands of adrenocortical cells containing *H. capsulatum* still intact in one area near the capsule. Many organisms within macrophages were also seen in the surrounding granulation tissue (figure 5).

The cervical, axillary, periaortic, and mesenteric lymph nodes were enlarged, firm, and discrete. Several showed gray, granulomatous areas on their cut surfaces; others were caseous. Many of the nodes were replaced by fibrous tissue. Necrotic areas were present only in the periaortic and mesenteric nodes. There were numerous yeast cells typical of *H. capsulatum* within macrophages, and giant cells were noted in all of the above nodes.

The brain weighed 1,375 gm. and was markedly edematous. On coronal sectioning, six spherical nodules ranging from 4 to 8 mm. in diameter were demonstrated within the cortex of the right frontal and parietal lobes (figure 6). A similar, larger lesion measuring 2.0 by 2.9 cm. in diameter was located in the right cerebellum. On microscopy, these nodules were seen to have necrotic centers surrounded by lymphocytes, epithelioid cells, and an occasional Langhans' giant cell. Numerous compound granular cells were engorged with characteristic yeast-phase cells of *H. capsulatum*. The meninges over one of these cortical lesions demonstrated inflammatory changes and contained numerous *Histoplasma* organisms.

FIG. 6. Brain, coronal section. Arrow points to cortical granuloma of *H. capsulatum*

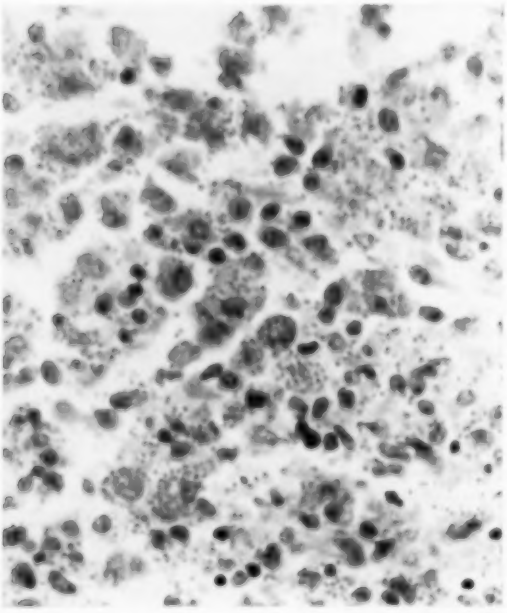

FIG. 7. Section through base of ulcer of ileum. Myriads of *Histoplasma* within macrophages in ulcer crater (top). (Periodic-acid-Schiff × 640)

FIG. 8. Section of prostate. Macrophages within glands and interstitium laden with *H. capsulatum*. (Periodic-acid-Schiff × 100)

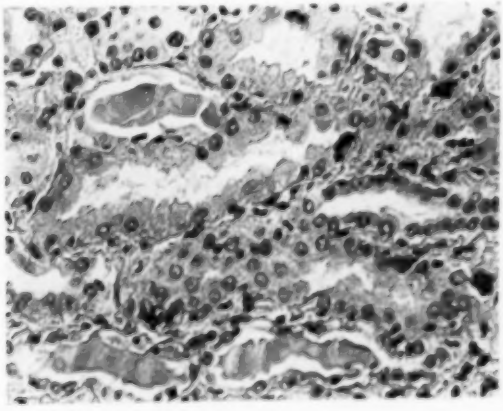

FIG. 9. Section of kidney showing tubular damage, casts, and regenerating epithelium. (Hematoxylin and eosin × 480)

Several irregular, circumferential mucosal ulcers, varying from 5 to 18 mm. in diameter and from 2 to 4 mm. in depth, were noted in the jejunum and cecum. One larger ulcer, 9 by 17 mm. in diameter and 4 mm. deep, surmounted the ileocecal valve. Myriads of *Histoplasma* were found in all layers of the ulcer; many were outside macrophages (figure 7). Solitary lymph nodes, Peyer's patches, and lymph spaces contained giant cells packed with organisms. The spleen contained tubercles with macrophages laden with fungi. The liver showed periportal fibrosis. Multiple sections of ribs, sternum, and vertebrae all contained giant cells engorged with yeast-phase fungi. The prostate was invaded by organisms seen within macrophages, both in glandular and interstitial tissue (figure 8).

The kidneys showed evidence of severe damage. The lumina of both proximal and distal convoluted tubules contained many pigmented casts. Desquamated epithelial cells, interstitial edema, and focal collections of inflammatory cells were seen. Several tubercles containing giant cells and intracellular *H. capsulatum* were also present in the interstitium.

The final anatomical diagnosis was: (*1*) disseminated histoplasmosis of the lung, adrenal, brain, liver, kidney, spleen, lymph nodes, bone marrow, small and large intestine, and prostate; (*2*) moderately advanced pulmonary tuberculosis of the right lung; (*3*) acute renal tubular necrosis; and (*4*) pulmonary emphysema.

DISCUSSION

In recent years the changing picture in the pathogenesis of adrenal insufficiency has been commented on by several writers (1, 2). Formerly, the majority of instances of adrenal necrosis were secondary to tuberculosis. With the gradual decline in mortality and morbidity from this disease, other agents have assumed a proportionately greater role in the genesis of Addison's disease. More recently, disseminated fungal infections have been recognized as causal factors in adrenal necrosis and Addison's disease (3, 4). It is the present writers' opinion that many of the cases now considered idiopathic adrenocortical atrophy in areas where infection with *Histoplasma* is extremely prevalent may ultimately be shown by appropriate staining and culture techniques to be secondary to this pathogenic fungus. Experience with the patient of the present report would further suggest that Addison's disease, secondary to necrosis of the adrenal gland by *Histoplasma*, may prove to be more refractory to conventional management than other forms of adrenal insufficiency.

Our knowledge and thinking regarding the significance of this fungal infection have undergone an interesting evolution in the five decades that have elapsed since Darling's original description of this disease in Panama (5). Earlier concepts stressed the serious prognosis associated with the infrequently recognized fatal case (6). More recently, Palmer, among others, directed attention to the possibility that a fairly widespread benign form of infection accounted for residual calcific lesions in nonreactors to tuberculin (7). Furcolow and co-workers have described the explosive epidemics that can be seen to arise from a common source of infection with primarily pulmonary involvement, usually associated with favorable prognosis (8). Christie has studied the problem of infection in childhood, and has demonstrated the presence of a primary minimal lesion very similar to that of tuberculosis (9). More recently, attention has been directed to the chronic, cavitary, pulmonary infection that often mimics pulmonary tuberculosis (10); and to its refractory response to chemotherapy (11). Present concepts of infection recognize three relatively distinct types: primary histoplasmosis, reinfection histoplasmosis, and progressive histoplasmosis.

The patient of the present report had progressive, disseminated histoplasmosis with myriads of yeast-phase fungi seen and recovered by culture from practically all organ systems of the body. Concurrently, he was reinfected with an adult type of pulmonary tuberculosis, which remained confined to the lung. The inconsistency of this host-

parasite relationship further points out the lack of fundamental knowledge in regard to factors that determine spread or localization of infecting agents. The failure to respond to repeated tuberculin skin testing, while multiplying tubercle bacilli are present within the lung, is seen quite often in adrenal insufficiency. It is of interest, however, that this patient responded to histoplasmin initially, thus supporting the views of Conant and others that *Histoplasma* produces a greater skin hypersensitivity than does *Mycobacterium tuberculosis* (12, 13). When retested with histoplasmin three weeks later, the skin test was negative and remained so. Cortisone therapy may possibly have influenced this phenomenon.

The fungal lesions in the brain closely simulated those of disseminated tuberculosis in distribution and gross characteristics. The presence of a localized area of meningitis overlying one such cerebral lesion simulated closely the tuberculous lesions described by Rich as evolving into tuberculous meningitis (14). The autopsy incidence of central nervous system invasion by *H. capsulatum* has been found by others to range between 10 and 25 per cent (15, 16, 17). However, the complication of overt meningitis has been extremely infrequent.

Therapy with 2-hydroxystilbamidine in fairly large dose (225 mg. daily) had little apparent effect on the fungal population of this host. The pathogenic yeast-phase organisms could still be recovered at will after four weeks of therapy. The immediate results of treatment with β-diethylaminoethyl fencholate in this patient appeared no better. At autopsy, myriads of pathogenic fungi were found throughout most of the body. The use of this agent in treating chronic cavitary histoplasmosis has been reported by others to have little apparent effect on the infection (11).

Close inspection of various organ systems in this patient failed to disclose lesions suggesting drug damage, with the exception of the previously mentioned lower nephron nephrosis. The specific relationship of either 2-hydroxystilbamidine, β-diethylaminoethyl fencholate, or recurring periods of shock to this end stage of severe renal damage can, at best, be only speculative. However, renal function tests were grossly abnormal preceding the antifungal therapy. It is hoped that more potent and less toxic agents will be forthcoming to aid in the treatment of the disseminated and often fatal form of histoplasmosis.

SUMMARY

A case of fatal disseminated histoplasmosis with Addison's disease and active pulmonary tuberculosis is presented. Therapy with 2-hydroxystilbamidine and β-diethylaminoethyl fencholate was unsuccessful.

SUMARIO

Enfermedad de Addison Asociada con Histoplasmosis Diseminada y Tuberculosis Pulmonar

Preséntase un caso de histoplasmosis diseminada con enfermedad de Addison y tuberculosis pulmonar activa. La terapéutica con 2-hidroxistilbamidina y fenocolato beta-dietilaminoetílico no surtió efecto.

RESUME

Maladie d'Addison associée à l'histoplasmose disséminée et à la tuberculose pulmonaire

Présentation d'un cas mortel d'histoplasmose associée à la Maladie d'Addison et à la tuberculose pulmonaire. Le traitement par la 2-hydroxystilbamidine et le fencholate de béta-diéthylaminoéthyle a échoué.

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Notes

THE EFFECT OF CYCLOSERINE ON GROWING AND RESTING TUBERCLE BACILLI

Clinical[1] and laboratory[2, 3] observations indicate that a new drug, cycloserine, exhibits antituberculous activity. For an understanding of the antibacterial effect of cycloserine on the tubercle bacillus, it is important to know whether it affects only growing or also resting bacteria.

The effect of cycloserine[4] on growing and resting tubercle bacilli was studied in the following experiment.

Mycobacterium tuberculosis, strain H37Rv, was cultivated in a Tween[5] albumin medium described by Schaefer.[5] This synthetic medium employs glucose as the sole source of carbon, and ammonium chloride as the source of nitrogen. After six days of incubation at 37°C. the bacteria were recovered by centrifugation and the cells were washed three times with the basal (containing no glucose) medium. The washed organisms were then suspended in basal medium and the concentration was adjusted to 1 mg. per ml. (wet weight). Four modifications of the basal medium were inoculated with 0.2 ml. of the above bacterial suspension for each 9.8 ml. of medium. The medium was modified as follows:

Medium *A*—Basal + 1 per cent glucose
Medium *B*—Basal + 1 per cent glucose + 40 γ of cycloserine per ml.
Medium *C*—Basal
Medium *D*—Basal + 40 γ of cycloserine per ml.

Five tubes of each modification of medium were incubated at 37°C. and the optical density (650 mu.) of the cultures was recorded at forty-eight-hour intervals for a period of twenty days. Colony counts were made on charcoal agar medium[6] at zero, three, six, ten, fifteen, and twenty days following inoculation. The agar plates were seeded with 0.3 ml. of a 10^{-4} dilution of the liquid cultures. The acid-fast property of the bacteria was determined at the end of the experiment by the use of the Ziehl-Neelsen technique.

The results of the turbidity measurements are presented in figure 1. It may be seen that, unlike isoniazid, which allows approximately one and one-half generations before growth is arrested *in vitro*,[5] cycloserine exerts bacteriostatic action almost immediately. The results of the colony counts are shown in table 1. It will be seen that the number of viable bacilli in the medium containing glucose and cycloserine would indicate a tuberculostatic rather than a tuberculocidal action. In contrast, isoniazid was shown[5] to be rapidly tuberculocidal in the presence, but not in the absence, of glucose. The bacilli remaining at the end of the experiment retained their acid-fast staining quality as reflected by the Ziehl-Neelsen technique.

In summary: The effect of cycloserine on tubercle bacilli *in vitro* was studied in the culture media with and without glucose as the sole carbon source. Cycloserine was found to be bacteriostatic in the presence of glucose. No significant bactericidal effect could be

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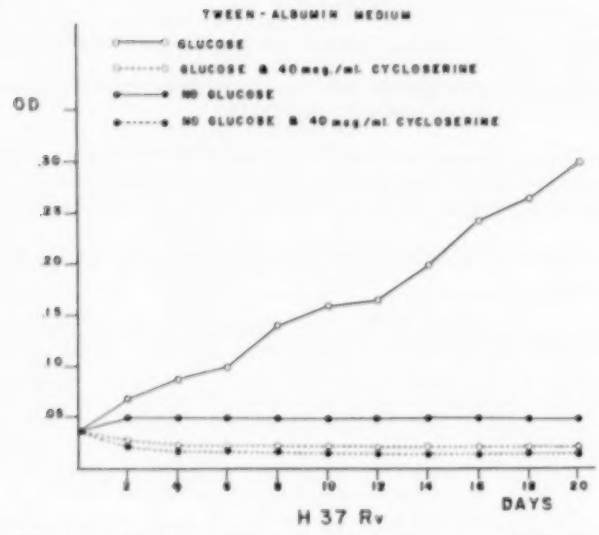

FIG. 1. Effect of cycloserine on the growth of *M. tuberculosis* (H37Rv) in the presence and absence of glucose.

TABLE 1

COLONY COUNTS OF TUBERCLE BACILLI (H37RV) EXPOSED TO CYCLOSERINE IN THE PRESENCE AND ABSENCE OF GLUCOSE AS THE CARBON SOURCE

Days of Incubation Before Plating	Medium A	Medium B	Medium C	Medium D
0	50	50	50	50
3	100	50	70	50
6	Innum.	40	70	40
10	Innum.	50	80	40
15	Innum.	40	70	30
20	Innum.	40	75	40

Innum.—colonies too numerous to count

detected either in the presence or absence of glucose. Cycloserine had no effect on the acid-fast staining properties of the organisms.

TUBERCULOSIS RESEARCH LABORATORY
VETERANS ADMINISTRATION HOSPITAL
WASHINGTON, D. C.

PAUL C. HUDGINS
ROBERT A. PATNODE
MARTIN M. CUMMINGS

August 8, 1955

A COMPARATIVE STUDY OF CULTURE AND GUINEA PIG INOCULATION IN THE ISOLATION OF M. TUBERCULOSIS FROM SPECIMENS OF HUMAN SOURCE

In recent years, with the development of better culture media, there has been a tendency to discard the use of the guinea pig for the bacteriologic diagnosis of tuberculosis. The purpose of this communication is to compare the laboratory results obtained from the use of artificial media and guinea pig inoculations. It is believed that the results serve to re-emphasize the important role of guinea pig inoculation in the isolation of *M. tuberculosis* from specimens of human source. The group of bacteriologic diagnoses designated as "positive" represents the isolation of individual patient-strains of *Mycobacterium tuberculosis* either on culture or by guinea pig inoculation. The pathogenicity for guinea pigs of the strains isolated has been utilized as the final criterion for diagnosis in doubtful cases.

For this investigation a total of 6,613 specimens was studied during the years 1948 to 1954, inclusive. Positive diagnoses were made on specimens from 447 patients. Most of the specimens were from untreated patients and were submitted to the Bacteriology Diagnostic Laboratory by the University Hospitals of the State University of Iowa. An occasional specimen was supplied by neighboring tuberculosis sanatoriums. The specimens included sputum, urine, bronchial aspirations, gastric washings, cerebrospinal and pleural fluids, biopsy tissues, pus from abscesses, and tissue taken at autopsy. When necessary the specimens were treated and concentrated in the usual manner. The specimens which did not contain other microorganisms were inoculated on the medium and injected into the guinea pigs untreated.

Two different culture media were used. From 1948 through 1950 Corper's potato medium[1] was employed, whereas from 1951 through 1954 the Holm[2] modification of the Löwenstein-Jensen medium was utilized.

One tube of culture medium and one guinea pig were inoculated for each specimen submitted for diagnosis. The media were incubated for six weeks at 37°C. with frequent observation for growth.

The guinea pigs were autopsied six weeks after injection. Organs showing gross infection were removed, and the acid-fast bacilli were observed microscopically. If inoculated culture medium showed no growth of tubercle bacilli and the guinea pig showed evidence of disease in a local node only, the node was removed, triturated, and passed to a second guinea pig for further study. If bacilli were isolated by culture and the guinea pig inoculation was negative, the cultured strain was tested for pathogenicity by inoculation into another guinea pig. In such circumstances, if the second pig inoculation resulted in progressive tuberculous disease the results were recorded as culture-medium–positive, guinea pig-negative, because of the initial findings.

The manner in which the results were classified for this study is indicated in table 1. It is interesting to note that a complete correlation of the results obtained with guinea pigs and culture medium was present in only 50.8 per cent of the cases. If guinea pigs had not been utilized, 35.1 per cent of the positive diagnoses would not have been made. Inoculation of culture media accounted for the isolation of 11.4 per cent of the strains which were negative by guinea pig inoculation. It is important to observe, however, that eighteen of the strains isolated on culture were nonpathogenic on guinea pig inoculation. A possible explanation of these nonpathogenic strains is that they had become attenuated during

[1] Corper, H. J., and Uyei, N.: J. Lab. & Clin. Med., 1938, *24*, 70.
[2] Holm, J., and Lester, V.: Pub. Health Rep., 1947, *62*, 847.

TABLE 1

ISOLATION OF M. TUBERCULOSIS FROM SPECIMENS OF HUMAN ORIGIN

Classification of the Results Obtained from 1948 through 1954

	Number	Per Cent
Positive guinea pig and positive culture medium	227	50.8
Positive guinea pig and negative culture medium	92	20.6
Positive guinea pig, culture medium liquefied or overgrown with organisms other than *M. tuberculosis*	36	8.0
Negative guinea pig and positive culture medium	51*	11.4
First guinea pig with positive local node only, passed to second guinea pig which was positive; culture medium negative	29	6.5
First guinea pig with positive local node only, passed to second guinea pig which was negative; culture medium negative	12	2.7
Total	447	100.0

* Eighteen of these isolates were shown to be nonpathogenic on guinea pig inoculation.

chemotherapy but, as previously pointed out, the great majority of the specimens were from previously untreated patients.

A comparison of guinea pig inoculation and Holm's modification of the Löwenstein-Jensen medium for the various specimens is illustrated in table 2. The results indicate that the guinea pig is superior to this medium when the specimens are tissues, pus, urine, gastric washings, and sputum. The culture medium was slightly superior to guinea pig inoculation for the isolation of *Mycobacterium tuberculosis* from cerebrospinal fluid and bronchial washings, although the differences were equivocal.

The results obtained from the comparison of Corper's potato medium are shown in table 3. Guinea pig inoculation was considerably more reliable than this medium, as

TABLE 2

ISOLATION OF M. TUBERCULOSIS FROM SPECIMENS OF HUMAN ORIGIN

An Analysis Comparing the Guinea Pig and Holm's Modified Löwenstein-Jensen Medium with Various Specimens, 1951 through 1954

Specimen	Number Tested	Positive by		Percentage by	
		Guinea Pig	Culture Medium	Guinea Pig	Culture Medium
Tissue and pus	62	55 (3)*	41 (1)†	83.9	64.5
Urine	57	50 (2)*	37 (6)†	83.2	54.4
Bronchial aspirations	14	12 (2)*	13 (1)†	71.4	85.6
Gastric washing	26	24	20	92.3	76.8
Sputum	88	75 (2)*	66 (6)†	83.0	68.1
Cerebrospinal fluid	15	13 (1)*	14	80.0	93.3
Pleural fluid and other aspirated fluids	15	13	10 (1)†	86.7	60.0
Total	277	242 − 10 = 232	201 − 15 = 186	83.8	67.1

* These numbers indicate the specimens in which the first guinea pig exhibited a positive local node only, which, when passed to the second guinea pig, was negative.

† These numbers indicate specimens in which the guinea pig was negative, the culture medium positive, and the strain thus isolated was nonpathogenic on guinea pig inoculation.

TABLE 3

ISOLATION OF M. TUBERCULOSIS FROM SPECIMENS OF HUMAN ORIGIN

A Comparison of Reliability Between the Guinea Pig and Corper's Potato Medium with Various Specimens, 1948 through 1950

Specimen	Number Tested	Positive by		Percentage by	
		Guinea pig	Culture Medium	Guinea Pig	Culture Medium
Tissue and pus	35	34 (1)*	13	94.3	37.6
Urine	40	36 (1)*	24 (2)†	87.5	55.0
Bronchial aspiration	5	2	4 (1)†	40.0	60.0
Sputum	35	31	22	88.6	62.8
Gastric washing	18	17	11	94.5	61.1
Cerebrospinal fluid	18	15	14	83.4	77.7
Pleural fluid and other aspirated fluids	19	19	11	100.0	57.9
Total	170	154 − 2 = 152	99 − 3 = 96	89.4	56.4

* These numbers indicate specimens in which the first guinea pig exhibited a positive local node only, which when passed to the second guinea pig was negative.

† These numbers indicate specimens in which the guinea pig was negative, the culture medium positive, and the isolate was shown to be nonpathogenic on guinea pig inoculation.

indicated by the data. It is also apparent that Holm's modification of the Löwenstein-Jensen medium was somewhat superior to the Corper potato medium in percentage of positive isolations.

Based upon the evidence from the present study, the guinea pig cannot be excluded from the routine bacteriologic diagnosis of tuberculosis without serious impairment of the efficiency of diagnosis. The literature[2-5] contains a diversity of opinion on this subject. As demonstrated by the evidence presented in this paper, neither the guinea pig nor culture medium can be regarded as completely reliable. It is true that if several tubes of culture medium were inoculated with each specimen the percentage of positive isolations for the medium would be higher. Likewise, the inoculation of several animals would presumably increase the per cent of positives in this category. However, the deletion of animal inoculation from the routine procedure would result in the loss of the guinea pig pathogenicity determination and, at the present time, guinea pig pathogenicity is an important part of the laboratory characterization of strains of *Mycobacterium tuberculosis*.

It is believed justified, therefore, to recommend that the use of both culture medium and guinea pig inoculation will result in the most accurate procedure for the bacteriologic diagnosis of tuberculosis.

STATE UNIVERSITY OF IOWA
SCHOOL OF MEDICINE
DEPARTMENT OF BACTERIOLOGY
IOWA CITY, IOWA

H. F. HASENCLEVER
A. P. MCKEE

May 27, 1955

[2] HOYT, A., HOLTSWART, F., KUNTZER, B., AND FISK, R. T.: J. Lab. & Clin. Med., 1939, *25*, 88.

[3] AMERICAN TRUDEAU SOCIETY: Am. Rev. Tubere, 1953, *68*, 951.

[4] LEUALLEN, E. C., AND CARR, D. T.: New England J. Med., 1955, *252*, 79.

LABORATORY INFECTION WITH HISTOPLASMA CAPSULATUM[1]

Accidental laboratory infections with *Histoplasma capsulatum* have been reported by several workers. This report concerns the exposure to *Histoplasma capsulatum* of 17 young women during their training in medical technology and one male graduate student during his work in agricultural bacteriology.

The students in medical technology were assigned to studies involving the handling of *Histoplasma capsulatum* in mid-February, 1953. All of the members of the class were present and carried out the same laboratory exercise. They prepared material for microscopic examination and transferred cultures from previously prepared cultures. These cultures had been planted in test tubes approximately four weeks before they were used by the class. As far as is known, there was no obvious break in technique nor was there subsequent contact with *Histoplasma capsulatum*.

Approximately two weeks later, one of the 17 students, F. F., had a minor illness and was seen in the Student Health Department.

F. F. had been ill for a few days with mild generalized aching and fever as high as 102°F. Physical examination was not revealing and the possibility of infectious mononucleosis was considered. However, neither the leukocyte count nor the heterophil antibody test gave any support for this diagnosis. As she improved quite rapidly, she was not seen again until the middle of March.

At this time, a routine chest roentgenogram had shown a very minimal amount of mediastinal lymphadenopathy. She was re-examined, but no other lymphadenopathy or splenomegaly was found. A flocculation test of hepatic function (Hanger's test) was three plus on March 31, 1953, and was still three plus on May 28, 1953. No diagnosis was made and the hilar adenopathy cleared in approximately three weeks. At the end of May F. F. reported the appearance of a few tender reddened areas on her shins. These were characteristic of erythema nodosum. The presence of a drug reaction, tuberculosis, or rheumatic fever seemed highly improbable. Because of the previous hilar adenopathy, the possibility of histoplasmosis was considered, although there was still no history of the laboratory contact with *Histoplasma capsulatum*. When her histoplasmin test was found to be positive, a complement-fixation study was requested from Dr. M. L. Furcolow. Only after the complement-fixation titer was reported as 1:2,048 was the information obtained that the entire class had worked with *Histoplasma capsulatum* in February, 1953. Blood cultures and gastric cultures were done in July, 1953, but no *Histoplasma capsulatum* was isolated.

None of the other students in the course had been aware of any illness. All had 14- by 17-inch chest roentgenograms taken three to four weeks after the probable laboratory exposure and the student, F. F., as previously mentioned, was the only one with any recognized abnormality. It seemed advisable to check the histoplasmin sensitivity status of the entire class as the prevalence of histoplasmin sensitivity among Wisconsin residents of college age is approximately 10 per cent. Four of the group had shown no reaction to histoplasmin in a routine testing in 1949. On July 15, 1953, the remaining 16 women of the class were tested with 0.1 ml. of a 1:1,000 solution of histoplasmin. All the tests were strongly positive. Blood for complement-fixation and precipitin tests was sent to Dr. Furcolow. There were 4 students in addition to F. F. whose serum yielded positive complement-fixation tests at titers of 1:256, 1:32, 1:16, and 1:8, respectively, and 4 whose serum gave complement-fixation tests reported as suspicious.

[1] Presented before the Medical Session, as part of *Section 6B*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 25, 1955.

No roentgenographic abnormalities were observed in the films obtained in July, 1953, or in subsequent films. There has been no evidence of clinical disease in any of these 16 women, except for patient F. F.

However, on May 20, 1953, shortly after F. F. had been seen because of erythema nodosum, a male graduate student in agricultural bacteriology, W. H., was seen.

This 25-year-old Australian had come to the University in September, 1952. His entrance 70 mm. chest photofluorogram was normal. He complained of headache, general malaise, and slight fever of about one week's duration. Physical examination was not revealing. As in the case of patient F. F., the possibility of an infectious mononucleosis was considered. The leukocyte count was normal except for an occasional abnormal lymphocyte. However, the heterophil antibody test and Hanger's flocculation test of hepatic function were negative. A chest roentgenogram on May 28, 1953, showed some increases in the peribronchial markings and a few fine nodular infiltrates, especially in the right medial base. Because of this change, W. H. was questioned about possible laboratory contact with fungi. He reported that he had transferred both *Blastomyces dermatitides* and *Histoplasma capsulatum* cultures three or four times in the preceding two months. Coccidioidin, blastomycin, and histoplasmin tests were performed and only the histoplasmin test was positive. Complement-fixation studies for blastomycosis and histoplasmosis were carried out. The former was reported as 1:2 and the latter as 1:32. Clinically, this student improved rapidly and felt entirely well after approximately two weeks of illness. The minimal chest roentgeno-

TABLE 1

Name	Histoplasmin Test July, 1953	Precipitin and Complement Fixation Titers						
		Precipitin July, 1953	Complement Fixation July, 1953	Precipitin August, 1953	Complement Fixation August, 1953	Complement Fixation September, 1953	Complement Fixation February, 1954	Complement Fixation January 1955
	mm							
F. F.			2,048*					
F. F.	20 × 15	20	256	5	32	16	8	0
L. B.	60 × 90	20	256	5	128	32	32	—
M. M.	50 × 60	0	16	5	8	2	0	—
J. S.	80 × 90	80	8	40	4	8	0	—
D. T.	55 × 80	0	32	0	32	32	4	—
B. F.	60 × 80	0	4	0	2	—	0	—
M. F.	70 × 80	40	2	10	4	—	8	—
M. L.	35 × 40	0	4	0	2	—	0	—
A. K.	50 × 100	10	Suspicious	0	0	0	0	—
C. B.	25 × 30	0	0	—	—	—	—	—
B. G.	60 × 90	0	0	—	—	0	0	—
B. S. G.	60 × 70	0	0	—	—	4	—	—
J. G.	50 × 70	0	0	—	—	—	0	—
K. P.	60 × 80	0	0	—	—	—	—	—
N. R.	50 × 80	0	0	—	—	8	0	—
M. S.	50 × 80	0	0	—	—	4	0	—
J. W.	70 × 100	0	0	—	—	4	4	—
W. H.	15 × 15		128	—	—	512†	32	0

* June, 1953.

† November, 1953.

graphic changes cleared rapidly and there has been no significant residual. Four gastric aspirations and several blood cultures taken during July and August, 1953, showed no *Histoplasma capsulatum*.

The histoplasmin skin tests, complement-fixation and precipitin tests are presented in table form (table 1). Six persons, including the 2 with minor illness, had positive tests. The serum from 8 women yielded complement fixations in a "suspicious" titer at some time during the year subsequent to the time of the laboratory exposure.

From the data obtained, it is believed that actual infection with *Histoplasma capsulatum* did occur although it has not been possible to recover the organism. The skin tests were much more marked than were the tests performed with the same antigen in the same dilution when it was used in a routine testing of students entering the University. This might indicate a recent conversion because of the greater sensitivity. The universal sensitivity in all 18 students would be highly improbable in a group of Wisconsin residents of college age.

Only 4 women had negative complement-fixation tests and in 2 of them the test was done on one occasion only, in July, 1953. The changing titers also supported the impression that infection had occurred. The extremely high complement-fixation antibody titer of the serum of F. F., in whom erythema nodosum was present, is very strong evidence that *Histoplasma capsulatum* was the causative agent. The serum of the other student, W. H., who also had a clinical illness, was likewise positive in a higher titer than the others. However, L. B.'s serum was positive at a titer of 1:256 when first tested, although she had had no illness that she could recall.

This pattern of sensitivity and antibody response is very similar to that seen with *Coccidioides immitis* infection.

In conclusion: Laboratory exposure to *Histoplasma capsulatum* may result in a high incidence of infection without clinical illness or roentgenographic evidence of pulmonary abnormality. High titers of complement fixation for histoplasmosis may occur in persons after *Histoplasma capsulatum* infection without any recognized illness. Erythema nodosum can occur in this setting as the result of *Histoplasma capsulatum* infection. *Histoplasma capsulatum* should be regarded as a hazardous organism and should be handled with appropriate precautions.

Department of Preventive Medicine
University of Wisconsin
Madison, Wisconsin

Helen A. Dickie
Marion E. Murphy

May 25, 1955

Correspondence

CHROMOGENIC ACID-FAST BACILLI FROM HUMAN SOURCES

To the Editor of The American Review of Tuberculosis and Pulmonary Diseases:

In a note which recently appeared in the REVIEW (Am. Rev. Tubere., 1955, *72*, 119), ten strains of "chromogenic acid-fast bacilli from human sources" were described as being insensitive to isoniazid (100 γ per ml.) *in vitro*. At least some of these strains were assumed by the authors of that report to have been agents of disease in the patients from whom they derived, and to be similar to, or identical with, the strains of "yellow bacillus" described by Buhler and Pollack (Am. J. Clin. Path., 1953, *23*, 363).

In addition to 584 bacteriologically proved (by culture) cases of pulmonary tuberculosis admitted to our hospital during the past three years, 6 patients from different parts of the United States have been demonstrated to have tuberculosis-like disease of the lungs attributable to mycobacteria of the yellow bacillus group (Am. J. Clin. Path., 1953, *23*, 363; J. Lab. & Clin. Med., 1954, *44*, 202). Pure cultures of these organisms, in large numbers, were repeatedly isolated from the sputum of these patients by methods previously described (Am. Rev. Tubere., 1954, *70*, 852). They were easily and immediately identified as such on culture of each of the first sputum specimens from these patients as routinely submitted for culture on the oleic-acid-albumin agar medium employed in our laboratories.

Drug-susceptibility studies on all of these strains, both by the "direct" method (on primary isolation) and by various "indirect" methods, have revealed them to be susceptible to isoniazid *in vitro* at concentrations between 0.5 and 1.0 γ of isoniazid per ml. *before treatment* with isoniazid.

The experimental animal pathogenicities of these strains have been studied in guinea pigs, mice (CF1 strain), and hamsters. The results of air-borne challenge infections (Proc. Soc. Exper. Biol. & Med., 1952, *80*, 105), believed by us to be most critical and reproducible, have shown them to be nonpathogenic for guinea pigs, highly pathogenic for mice, and moderately pathogenic for hamsters. Two of these strains were also injected by the intravenous route into rabbits and tuberculin-negative chickens; they proved to be nonpathogenic for these hosts.

As a result of our studies on these strains, we suggest that the chromogenic strains studied by Tarshis and associates (Am. Rev. Tubere., 1955, *72*, 119; and 1952, *65*, 278, 289, 302) are not pathogenic mycobacteria of the "yellow bacillus" type encountered by Buhler and Pollack, by Timpe and Runyon (J. Lab. & Clin. Med., 1954, *44*, 202) (Types I and III), and at this hospital, as described here. Therefore, it would seem unwise to conclude that the photochromogenic yellow bacilli are highly resistant to isoniazid. Indeed, in 3 of our patients infected with such strains who were treated with isoniazid alone, 16 mg. per kg. per day (plus pyridoxine), clear-cut chemotherapeutic responses were initially obtained, both clinically and bacteriologically.

DEPARTMENT OF RESEARCH & LABORATORIES
NATIONAL JEWISH HOSPITAL
DENVER, COLORADO

G. MIDDLEBROOK
M. L. COHN
R. OESTREICHER

DEPARTMENT OF MICROBIOLOGY
UNIVERSITY OF COLORADO SCHOOL OF MEDICINE
DENVER, COLORADO

August 2, 1955

INTRODUCTION OF ARTIFICIAL PNEUMOTHORAX

To the Editor of the American Review of Tuberculosis and Pulmonary Diseases:

It has been called to my attention that a statement in a recent article by Clarke, Shipman and Galbraith, "Introduction of Artificial Pneumothorax" (AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES, April, 1955) conveyed the impression that we differed from the position taken by Drs. Dooneief and Piccagli in their article published in the American Review of Tuberculosis, 1949, *60*, 557.

The reference number was misplaced and therefore should have read "have called attention to the subject" and not "take issue with the thesis that all initial pneumothoraces must be traumatic." This change of reference, therefore, would make our thoughts appear to be in agreement. Naturally we regret this, and wish to take this opportunity to clear our position which is substantially the same as Drs. Dooneief and Piccagli.

Very sincerely yours,
ROBERT W. CLARKE

490 POST STREET
SAN FRANCISCO
CALIFORNIA

August 9, 1955

Books

A Textbook of Medicine (Ninth Edition). Edited by Russell L. Cecil and Robert F. Loeb. Associate Editors: Alexander B. Gutman, Walsh McDermott, and Harold G. Wolff. Cloth. Pp. 1,786, W. B. Saunders Company, Philadelphia, Pennsylvania, and London, 1955, Price $15.00.

When a text reaches its ninth edition and attains a length of 1,800 pages it can no longer be regarded simply as a book or even an encyclopedia. Rather it has become an institution. In a certain sense it is like a school of medicine, and the analogy is strengthened in this case by the fact that, like a school, the text has what is essentially a medical faculty. One hundred and seventy-two authors have contributed articles; the list includes the most distinguished American internists.

The editors, Russell L. Cecil and Robert F. Loeb, and the associate editors, Alexander B. Gutman, Walsh McDermott, and Harold G. Wolff, have rendered an outstanding service to the medical profession in compiling this magnificant sequence of chapters. Some fifty new sections have been included in the ninth edition, which appears only four years after the eighth. In the material presented for the first time are treatises on Coxsackie viral infections by Robert J. Heubner, epidemic hemorrhagic fever by David P. Earle, nonsyphilitic treponematoses by Thomas B. Turner, Colorado tick fever by Lloyd Florio, pyridoxine deficiency by Tom D. Spies, cystic disease of the lungs by Herbert C. Maier, asbestosis by William S. McCann, senile heart disease by Hugh J. Morgan, and scleredema by A. McGehee Harvey. Rather remarkably, atherosclerosis has been elevated for the first time to the dignity of a section; it is treated in a scholarly discussion by David P. Barr as a disease of metabolism "so widely distributed as to suggest a defect inherent in mankind."

Readers of the American Review of Tuberculosis and Pulmonary Diseases will naturally be especially interested in the handling of tuberculosis and pulmonary disorders. The section on tuberculosis, as in past editions, is ably presented by J. Burns Amberson. It is not out of place to point out that one of the chief values in the presentation is its setting in its proper place as a segment of internal medicine. Such chapters, like medical societies, can suffer from too strict specialization and compartmentalization. Tuberculosis is here treated in relatively generous extent as one of the large group of bacterial diseases, with a fine balance of basic bacteriology and pathology, specific therapy, and consideration by organ systems. Although of necessity condensed, the section runs to fifty pages. This liberal provision is noteworthy in the light of the space afforded other diseases, e.g., two well-concentrated sections on diseases traditionally accorded great length in medical texts, malaria, by L. T. Coggeshall, and syphilis, treated in three separate articles by Walsh McDermott, Hugh Morgan, and Harry C. Solomon, which are comprised within eight and thirty-two pages respectively. The complaint, frequently voiced, that tuberculosis is now being accorded less than its due cannot be made of this text.

Appropriate authorship is one of the best guarantees of reliability and trustworthiness. The physicians who have handled various sections on diseases of the chest are leaders in their fields. Incidentally they are all long-time members or close associates of the American Trudeau Society, and therefore personally well known to readers of the Review. In this text are sections on diseases of the pleura and pneumothorax by John B. Barnwell, on diseases of the bronchi and mediastinum by Carl Muschenheim, on pulmonary function and circulatory and mechanical dysfunction of the lungs by Dickinson W. Richards,

on abscess and carcinoma of the lung by Herbert C. Maier, on pneumonoconiosis by William S. McCann, on empyema by William S. Tillett, and on sarcoidosis by William S. Middleton.

The pulmonary and other mycoses are well treated in a series of separate sections by David T. Smith. Phthisiologists will be especially interested in the articles on coccidioidomycosis and histoplasmosis. Tularemia is treated in a concise chapter by Karl F. Meyer.

The subject matter of the text is brought together comprehensively in an unusually detailed index prepared by Natalie J. Hoyt, who is credited also with the monumental task of proofreading and office editing. The volume is published in handsome format, of which the W. B. Saunders Company may justifiably be proud.

Esmond R. Long

Prolonged and Perplexing Fevers. By Chester S. Keefer and Samuel E. Leard. Pp. 248, Little, Brown & Company, Boston, Massachusetts, 1955, Price, $5.50.

The differential diagnosis of illness manifested principally by fever has fascinated physicians through the ages. Since the development of the clinical thermometer, many distinguished clinicians have attempted to formulate an orderly diagnostic approach to the patient with protracted fever of obscure origin. Articles written by Cabot in 1907, and by Alt and Barker and Hamman and Wainwright in the nineteen thirties, stand as classics which are read by each new group of house officers who are faced with this difficult clinical problem. In recent years, the accurate diagnosis of patients with perplexing fever has become increasingly important as new therapeutic tools have appeared on the scene. The development of antimicrobial drugs, chemotherapeutic agents of use in the management of some malignancies, and advances in surgery which allow a more aggressive approach to certain localized infections and new growths have prompted physicians to give increasing thought to methods of approach which may help to reduce the residua of cases which remain classified as "fever of unknown origin."

In an attempt to meet this problem, Drs. Keefer and Leard have assembled and analyzed their experience with patients manifesting prolonged fever in whom the diagnosis was originally inapparent. They have limited their discussion to cases in which fever has persisted for two weeks or longer, and have attempted to stress the types of clinical disorder in which the cause may remain undisclosed for long periods of time. The subject matter is arranged on the basis of clinical disease entities and these have been grouped in order of their relative frequency in producing problems of obscure fever. The initial section is devoted to a review of the variations which may be seen in normal body temperature and a discussion of diagnostic procedures which have a place in a planned approach to the problem of perplexing fever. Infectious fevers are considered in the succeeding section, with a discussion of specific etiologic agents commonly responsible for cases of obscure fever and of local sites of infection which may remain clinically silent and unrecognized for long periods of time. The closing section is devoted to an analysis of noninfectious causes of fever. Tumors frequently associated with temperature elevations are discussed in some detail. Blood dyscrasias in which fever is a common finding are enumerated, and less common clinical syndromes such as iodism, metal fume fever, and Weber-Christian's disease, in which prolonged fever may be a prominent symptom, are briefly considered. There is frequent use of specific case reports to illustrate the evolution of the clinical entity under discussion in patients initially presenting problems in prolonged fever.

Throughout the book, the authors have stressed the fact that obscure fever is most frequently due to a common, well-known disease process running an atypical course rather than exotic disease unfamiliar to the average physician.

The authors have compressed an impressive amount of clinical material into this small volume. It is difficult to know how much detail on diagnostic clues which may be detected at the bedside should be included in such a volume but, in the opinion of this reviewer, a fuller discussion of the subtler clinical features of syndromes producing obscure fever would have been worth while. The discussion of many disease entities is too brief to allow the reader to formulate his own concepts of the clinical features which might point toward the correct diagnosis. Also, the case reports fail to give enough information to allow the reader to reach the same diagnostic conclusions as those presented by the authors with any degree of certainty. The section on local septic infections fails to mention the problems of obscure fever which have arisen with the widespread use of antimicrobials; for example, localized intra-abdominal abscesses about the biliary tree and liver secondary to unrecognized perforation of the gall bladder or appendix during antimicrobial therapy. The extreme variations in the septic fever seen with local infections in or about the liver and the rarity of positive blood cultures in intra-abdominal infections drained by the portal vein, both important diagnostic leads, do not receive consideration.

The reviewer would have liked to gain a clearer impression of the precise way in which Drs. Keefer and Leard approach a difficult problem of prolonged fever and the ways in which they define, limit, and focus their laboratory investigations. Such an analysis might well have been included as a final summarizing section in their book. The problem in present day practice is generally not what investigative procedures should be performed, but rather what laboratory tests can be properly omitted on the basis of thoughtful analysis at a clinical level. It is recognized, however, that there is no satisfactory answer in generalities to this problem of wise selectivity which concerns physicians of the present day. This book by two experienced clinicians focuses on an area of great interest to all who are dealing with the care and management of patients in clinical medicine today.

David E. Rogers
New York, New York

As Perfuracoes de Ganglios Tuberculosos para a Arvore Traquiobronquica. By Thome George Villar. Pp. 200 with illustrations. Dissertacao de Doutoramento Apresentada a Facultade de Medicina de Lisboa, Lisbon, 1954.

This monograph is based primarily on 130 cases which were carefully studied by the author clinically, roentgenographically (including in most cases, tomography), bacteriologically and, in all cases except one, bronchoscopically.

As the title indicates, it deals with the perforation of tuberculous lymph nodes through the tracheobronchial tree. There are thirteen chapters, an appendix, and a bibliography. The first is a brief historical outline of the knowledge of this aspect of tuberculosis from the early observations of Laennec to the more modern ones of Schwartz, Lemoine, Dufourt, and others. Subsequent chapters discuss the normal anatomy of the intrathoracic lymph nodes as related to tuberculous infection, the physiopathology of perforating tracheobronchial tuberculosis, and the pathologic anatomy of these perforations. Each chapter is introduced by a historical review of the literature pertinent to the discussion, followed by an exposition and discussion of the author's own experience.

The chapter on the clinical aspect of these perforations emphasizes the paucity of symptomatology in many of the cases in which the diagnosis is made only incidentally in the course of bronchoscopy. On the other extreme of the clinical spectrum is the acute syndrome with dyspnea and cyanosis which requires immediate relief of the obstruction to prevent fatal asphyxia.

The chapter on the roentgenography of these perforations discusses lucidly the patho-

genesis of the various roentgenographic pictures produced, based on the literature and on the author's own material. Seventy-seven of the author's cases were studied by tomography and thirteen by bronchography.

The endoscopic aspects are discussed in a chapter which is illustrated by two color plates showing twenty-four views of various types of endobronchial lesions as seen through the bronchoscope in the course of this study. This chapter is concise and informative. Two chapters are devoted to complications, prophylaxis, and therapy of endobronchial lymph node perforations. Treatment is discussed from both the medical and surgical standpoints. The last chapter consists of a summary which in reality is a comprehensive but succinct synthesis of the whole problem.

The appendix is a well-organized table which summarizes the data on each of the author's 130 cases with all the pertinent clinical, roentgenographic, bronchoscopic, bacteriologic, and therapeutic data under appropriate headings. The bibliography is fairly complete, with 231 references to this rather specialized problem.

The monograph is well printed on good paper. The illustrations are clear and well chosen. The material is well presented and should be of interest to all students of tuberculosis. This reviewer knows of no comparable monograph on the subject published in the English language. The text of this book is in Portuguese.

F. Perez Pina
Waltham, Massachusetts

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Röntgen-Grobstrukturen des Thorax. By Heinrich Eschbach. Pp. 270, Georg Thieme, Leipzig, Germany, 1953, Price, D 30.

Wish I Might. By Isabel Smith. Pp. 234, Harper & Brothers, New York, New York, 1955, $3.00.

Veterans Administration Technical Bulletins Series 10, Vol. VII, 1954. Veterans Administration, Washington, D. C., 1955.

Cuarto Congreso Argentino de Tisiologia. Pp. 744, Las Sociedades de Tisiologia del País, Mar del Plata, Argentina, 1955.

L'Isolement du Bacille Tuberculeux a Partir des Produits Pathologiques Surinfectés. By Jean Audrin. Pp. 63, Plancher, Bonneville, France, 1955.

Pulmonary Resection for Tuberculosis. By Poul Ottosen. Pp. 166, Universitetforlaget I Aarhus, Aarhus, De mark, 1955, Price $3.00.

Tratamiento de la Meningitis Tuberculosa y de la Tuberculosis Pulmonar Aguda. By Juan Torres Gost. Pp. 122, Espasa Calpe, S. A., Madrid, Spain, 1955.

The Josiah Macy, Jr. Foundation 1930–1955. Pp. 174, Corlies, Macy & Company, Inc., New York, New York, 1955.

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American Trudeau Society

Medical Section of the National Tuberculosis Association

TUBERCULOSIS HOSPITAL ADMINISTRATION

Minimal Medical and Administrative Standards

The same fundamental principles which apply to the administration of general hospitals are applicable in the organization and operation of tuberculosis hospitals.[1] For details, standard texts should be consulted. Certain modifications are necessary, however, because of the long-term stay of chronically ill patients and the communicable nature of their disease.[2] The purpose of these standards is to encourage the best care of tuberculosis patients and they apply principally to the minimal standards for medical administration. Standards for nonmedical administration should be in keeping with good business and hospital practice. The number of beds needed, the site, the architectural requirements for medical, surgical, and service facilities, the personnel quarters, utilities, and so on, should be in accordance with accepted modern standards.[3, 4, 5] The Committee on Tuberculosis Hospital Administration recommends that, for the construction of a new hospital, a minimum capacity of 100 beds be considered and, where possible, such smaller units be connected with local general hospitals. In the interest of efficiency and economy of operation, a capacity of not less than 200 beds is preferable in communities where the death rate and morbidity of tuberculosis justify the larger hospital. The smaller the institution, the greater will be the proportionate cost of salaries for department heads and the greater the difficulty in obtaining well-qualified, full-time medical superintendents, staff members, and consultants necessary for the proper functioning of the service.

I. ORGANIZATION

The primary function of every hospital is to serve the best interests of the patient in keeping with the best medical care and treatment possible to ensure recovery. A governing board of trustees, managers, or directors is advisable for the formulation of the policies of the hospital. In the case of tax-supported institutions, a policy-making board or official is specified by law.

The medical superintendent should be solely responsible to the board for the management of the hospital and for the medical care and treatment of its patients. He must, therefore, be given full authority by the board. All officers and employees should be appointed by him, or subject to his approval, and be answerable to him.

Successful operation of a hospital depends upon the integration of its medical and nonmedical activities. The organization should permit distinct delegation of responsibilities. The medical superintendent, well trained in the treatment of the sick and interested

[1] Standards for Hospital Accreditation, Joint Commission on Accreditation of Hospitals, Chicago, April 19, 1953.

[2] Standards for Tuberculosis Hospitals, Manual of Hospital Standardization, American College of Surgeons-American College of Chest Physicians, preliminary draft.

[3] AMERICAN TRUDEAU SOCIETY: Tuberculosis Hospital—2100 bed capacity, National Tuberculosis Association, 1945.

[4] AMERICAN TRUDEAU SOCIETY: Tuberculosis Hospital Planning and Construction, National Tuberculosis Association, 1945.

[5] UNITED STATES PUBLIC HEALTH SERVICE: Planning and Construction of Hospitals, 1947.

in the solution of medical problems, should delegate authority to a business manager in the administration of the nonmedical affairs of the hospital, and should hold him accountable for efficient performance. Conferences between these two should be frequent in order to enable the superintendent to keep in touch with significant developments and to guide in matters of policy. In such circumstances the integrity, ability, and full cooperation of the business manager are of the highest importance.

The successful operation of a hospital further depends on essential basic factors:

1. Sufficient funds should be made available to carry on the work successfully. Insufficient funds result in either a decrease in the number of patients treated or a lowering of the quality of medical care and attention given. Either is poor economy.

2. Sound business principles should be employed at all times. The operation of a hospital today fits into the realm of big business, and modern up-to-date business methods which do not lose sight of the fundamental aim of patient care should be practiced at all times to ensure success.

3. The administration of the hospital should be free from political interference. The appointment of the medical superintendent should be in accordance with sound civil service and career opportunity principles. A carefully selected, cooperative board of trustees, managers, or directors, or an official charged with this duty, who will carefully consider the recommendations of the medical superintendent, offer advice, and give backing and support to the medical superintendent, is of paramount importance.

4. Since the primary purpose of the hospital is the care and treatment of patients, the medical superintendent should be solely responsible to the board. Division of authority should not be encouraged or tolerated. Division of authority renders an injustice to all persons concerned and to the community which the hospital strives to serve, and may lead eventually to bickering, pettiness, scandal, and unfavorable publicity.

5. The tuberculosis hospital is an important instrument of tuberculosis control. The treatment of pulmonary tuberculosis is more apt to be successful if initiated in the hospital rather than if treatment is carried out in the home. To function at maximum efficiency, the hospital must be correlated with other agencies concerned with the control of tuberculosis within the community in order that the care of the patient may extend from the time of diagnosis through hospitalization into the period of aftercare until ultimately the patient is re-established as an independent, functioning member of the community. Local health departments should be notified routinely of admission and discharge of patients. They should be furnished with appropriate case summaries on discharge.

II. MEDICAL STAFF

The medical superintendent should be a reputable licensed physician with at least three years' experience in a recognized tuberculosis hospital and preferably well versed in the field of tuberculosis control. In hospitals of 100 or more beds, the position of medical superintendent should be full time. For hospitals of less than 100 beds, the medical superintendent should be full time but with the privilege of outside practice.

There should be, in addition to the medical superintendent, at least one full-time physician for the first 100 hospital patients, and one additional full-time physician for each 50 additional patients or major fraction thereof. This ratio does not include pathologists or roentgenologists.

Where the hospital assumes entire responsibility for the tuberculosis control service in the area it serves, there should be, beyond the physicians required for the medical administration of the hospital, additional medical personnel to conduct outpatient and clinic diagnostic and follow-up service and treatment.

Each member of the permanent medical staff should be a licensed physician or eligible for license and, preferably, should have served an internship in a general hospital.

The service of consultants in internal medicine, general surgery, and in the medical and surgical specialties should be utilized. In the larger hospitals, planigraphy, pulmonary function tests, laryngology, bronchoscopy, and thoracic surgery should be a part of the over-all, full-time diagnostic and treatment services. In the smaller hospitals these facilities should be made available through the services of consultants or by arrangement with other hospitals where such work is done.

Meetings of the medical staff, including consultants if possible, should be held regularly, preferably weekly, to discuss problems of diagnosis, treatment, and discharge of patients. It is also advisable to stimulate interest through seminars, clinico-pathological conferences, and journal clubs.

Medical education, teaching, and research should be encouraged. For purposes of study and reference, there should be an amply supplied medical library.

The medical administration should maintain a cooperative relationship with local medical schools, health departments, tuberculosis associations, and with the practicing physicians in the community. Contact with physicians from other hospitals and teaching centers should be encouraged and special training of interns and residents of other hospitals arranged whenever possible.

The attendance of the medical superintendent and other members of the medical staff at national and regional medical meetings should be subsidized. Such meetings provide opportunities for the physicians to obtain knowledge from the formal papers presented and also for invaluable private discussions with their colleagues. With this background the medical staff is in a far better position to keep abreast of recent developments than could be acquired by merely reading medical journals. This would result in better service to patients.

III. MEDICAL SERVICES

Every patient should be seen by a physician within twenty-four hours of admission and immediately if the patient is acutely ill. Complete confidence of the patient should be sought by the permanent staff physician and a good patient-physician relationship established.

The history and physical examination should be completed if possible within forty-eight hours of the patient's admission. The initial physical examination should be complete, with special consideration given to the chest and upper respiratory tract.

Routine laboratory tests and any other procedures indicated should be ordered at the time of the initial examination.

The patient should be told that, as soon as the examinations have been completed, including roentgenographic and laboratory findings, his case will be considered at a staff conference, following which he will be given a frank and honest evaluation. At that time the outline of planned treatment and its duration should be discussed with him, including the possibility of surgery if bed rest, chemotherapy, and other measures are not completely effective within a reasonable time during the hospital stay.

Patients who are confined to bed should be visited by the physician as often as necessary, but at least daily. All other patients should be seen by the phsyician at least twice a week. Ambulant patients should be seen as often as necessary but at least once weekly by the physician and daily by the nurse in charge.

Temperature, pulse, and respiration should be taken at least three times daily during the first two months of drug therapy, throughout any febrile phase, and thereafter three times daily one or two days of every week or two weeks.

Patients should be weighed on admission, as indicated during the course of treatment, and upon discharge.

Physical examination of the chest should be repeated as frequently as indicated, depending upon the particular conditions present and the clinical judgment of the physicians. The findings should be recorded.

Chest roentgenographic examination should be repeated at least every two months if the lesion has recently been unstable, and more often if necessary. After stability has been reached, the interval between roentgenographic examinations may be three months or more for patients under custodial care. For ambulant patients on graduated exercise and work as rehabilitation, the examinations should not be more than three months apart.

Progress notes regarding the patient's condition should be made at the time of each physical or roentgenographic examination and at sufficiently frequent intervals to record significant changes in his clinical course.

Plans for rehabilitation should be integrated with treatment from the start.

Treatments of all kinds, general and special, including diet and the regulation of physical activities of patients, should be prescribed and supervised by a physician. Standing orders for drugs and other treatment should be for a stated period and then, if necessary, renewed.

Strict bed rest should be available for all patients who need it, and definite periods of rest for all others should be a part of the hospital routine. The amount and degree of rest should be prescribed for each patient in detail with all permitted activities and restrictions definitely specified.

Facilities should be available for all indicated therapy, including antimicrobial agents and surgical procedures, in order that the particular treatment best adapted to a given case may be chosen freely, instituted promptly, and without regard to the patient's ability to pay.

All patients receiving pneumothorax or pneumoperitoneum should be fluoroscoped before each refill, as adequate roentgenographic guidance is essential to successful and safe management. In the course of such treatment, periodic review is necessary to determine the optimal time for its discontinuance or the substitution of other treatment. There should be a regular system for the periodic review of all cases at a conference of the entire medical staff. Such staff conferences should be held preferably once a week at which time newly admitted cases are considered; diagnostic problems may be discussed; present treatment, including antimicrobial drug regimens, approved or modified; and future treatment, including surgery, recommended.

Associated tuberculous and nontuberculous conditions should receive prompt and appropriate attention. Facilities should be available for aid in differential diagnosis.

Adequate dental services should be furnished at the hospital.

The medical records of patients should include the following: admission medical and social history; results of physical examinations; roentgenographic and fluoroscopic interpretations; laboratory findings; treatments given; reports of consultations and staff meetings; progress notes; surgical and anesthetic data; nurses' notes; temperature, pulse, and respiration charts; diagnosis on admission and discharge; and results of post-mortem examinations. All entries should be dated and signed.

The clinical classification of patients on admission and discharge should be made in accordance with *Diagnostic Standards* of the National Tuberculosis Association.

When appropriate, the attention of patients should be called to the existing state laws and local ordinances regarding isolation and quarantine of uncooperative, infectious, tuberculous patients who leave the hospital against medical advice, in order to discourage such irregular discharges.

Patients who are not acutely ill and who refuse to cooperate in treatment might well

be transferred to an "up" or ambulatory ward as "good chronics" or "maximum benefit cases" in order to release beds needed for the active treatment of acutely ill patients.

IV. EDUCATION OF PATIENTS AND HOSPITAL PERSONNEL

A planned program of patient education is essential. In the early phase of treatment, it aids the patient in his adjustment to the hospital and helps secure his cooperation in the routines devised to aid in his recovery and protect the health of others. Individual instruction in the demonstration of the techniques that will protect others should be intensive and re-taught as needed, so that it will become second nature for the patient to observe personal hygiene to prevent dissemination of tubercle bacilli. Education should be a function of every member of the hospital staff. Although the burden falls most heavily on the physician and nurse, the social worker, occupational therapist, and rehabilitation counselor have important roles. The program should be a continuing one and, except for the acutely ill, may be on a group basis to impart facts leading to the patient's better understanding of his own disease and everything he needs to know about tuberculosis, including its cause, prevention, and treatment. General health education and nutrition should be included. A variety of teaching aids should be available, including books, pamphlets, posters, patients' newspaper, movie films, and hospital radio. Ways should be devised to include foreign language groups in the program. Through integration with community resources, the educational program can be extended to the family and visitors of the patient.

An orientation and instruction period should be provided for all new physicians, nurses, attendants, orderlies, maids, and volunteer workers. This orientation should be given before assignment to ward duty to ensure acquaintance with the basic procedures of the work—protective measures and hospital policies and practices regarding the care of the tuberculous.[6, 7, 8]

V. THE CARE OF CHILDREN

Children with clinically active tuberculosis should be treated in a separate building or in a separate ward of the building for adults. Provision should be made for supervised play and for education so that, after discharge, they may take their place in the community with children of their age.

VI. ROUTINE LABORATORY PROCEDURES

With the use of antimicrobial agents in the treatment of tuberculosis, routine laboratory procedures have come to play a more important role than in the past. It is important to know whether a patient admitted to a hospital or sanatorium has normal blood and urine. In some instances it is essential to know that he has normal kidney and liver function, since some of the drugs used in modern therapy may have an adverse effect upon a patient with pre-existing liver or kidney damage. It is recommended, therefore, that a complete leukocyte, erythrocyte, and differential cell count be done, along with an estimation of the amount of hemoglobin, and a serologic test for syphilis. Recognized tests for hepatic and renal function should be performed when indicated.

[6] Patient Education at Rutland Heights, National Tuberculosis Association, 1950.

[7] Patient Education and the Hospital Program, Veterans Administration Technical Bulletin, TB 10-88, April 27, 1953.

[8] A Patient Education Program for the Tuberculosis Patient in the New York Hospital, New York Tuberculosis and Health Association, New York 16, 1953.

Examination of sputum or gastric contents by culture for tubercle bacilli should be done on all newly admitted patients and, when positive, the drug susceptibility of the recovered bacilli to streptomycin, isoniazid, and PAS—or to any other antituberculosis drug that may be indicated for therapy—should be tested. During treatment with antituberculosis drugs, the susceptibility of recovery tubercle bacilli should be determined from time to time. The approved laboratory methods recommended by the Laboratory Subcommittee of the Medical Research Committee of the American Trudeau Society should be used as a guide and should be referred to regularly, since they are revised from time to time to meet the ever-changing laboratory requirements needed to control the use of drugs in the treatment of tuberculosis.

By present-day laboratory methods, tubercle bacilli are now found in the sputum and gastric contents of a large proportion of tuberculous patients. The clinician should interpret the reports in the light of the total clinical picture. For guidance in therapy, discharge, or follow-up, he must relate the laboratory report to the rest of the available data. The laboratory should report the method employed as well as the result of the test. This gives the clinician additional valuable data since sputum found to be positive repeatedly by direct smear, as compared to sputum positive by culture of gastric washings only, may have completely different significance to the physician in charge of the case.

All newly admitted patients in whose sputum or discharges tubercle bacilli are not found should be tuberculin tested by the intracutaneous method, and it is desirable that they be tested for fungal infection.

Special attention should be given to the so-called "negative" sputum or gastric contents of patients who are, or recently were, receiving antimicrobial therapy, as such therapy sometimes causes a transient disappearance of the tubercle bacilli. Only after the lapse of two to three months following discontinuance of such treatment can sputum and gastric contents findings be regarded as truly negative for tubercle bacilli.

A chemical and microscopic examination should be made of a first morning specimen of urine of newly admitted patients. All specimens which show albumin, erythrocytes, or leukocytes, or a combination of these, should be examined for tubercle bacilli by culture. If negative, urinalyses should be repeated as indicated, but at least every four months.

Careful examination for tubercle bacilli should be made of all body exudates or biopsy specimens when indicated and in accordance with recommended laboratory procedures. If tubercle bacilli of bovine origin are suspected, animal inoculation of sputum, gastric contents, urine, or any other suspected material should be done in addition to culture.

All surgically resected lesions should be studied and cultured for tubercle bacilli. If found to be positive, resistance studies should be made.

Every effort should be made to obtain permission for autopsy of patients who have died at the hospital and to study the bacteriology and pathology of lesions removed at autopsy.

VII. NURSING SERVICE

The average bedside nursing time required per patient during each twenty-four hours depends upon the classification of the patient. Tuberculous bed patients require essentially the same routine nursing care as acute general medical and surgical patients. Orthopedic and recently operated surgical cases require additional nursing time, varying with the number and variety of special procedures which are a part of the nursing care. Studies[9, 10] have shown that patients on strict bed rest require approximately 3.4 hours

[9] A study of the nursing care of tuberculosis patients, Am. J. Nursing, 1938, *38*, 1021.

[10] Cues to Staffing Tuberculosis Units in Hospitals, National Tuberculosis Association, 1952.

of nursing service per patient per twenty-four hour day. Those on less strict bed rest require from 2 to 2.17 hours; semi-ambulant patients require approximately 1.5 hours, and ambulant patients approximately 0.5 hour per patient per twenty-four-hour day. The foregoing is on the basis of nursing hours required per patient, and the number of nurses employed annually to provide such coverage must include relief for days off, vacation, illness, and emergency absences. The calculated ratio of nursing service to patients includes the services not only of registered nurses, but those of licensed, practical nurses and trained nursing aides.

VIII. HEALTH PROGRAM FOR HOSPITAL PERSONNEL

A well-controlled health program designed to protect and improve the general health of all employees is essential for the control of tuberculosis in hospital personnel.[11] The risk of contracting tuberculosis can be significantly minimized if proper precautions and good living and working habits are observed. All employees should have a pre-employment complete physical examination, tuberculin test, and chest roentgenographic examination. All personnel who come in contact with patients or work in patients' rooms, laboratories, or are otherwise exposed to tuberculosis, should, if tuberculin-negative, receive BCG vaccination. They should be encouraged to observe good personal health practices in order to keep their resistance at a high level. They should not work more than eight hours daily and should have at least one day off out of every seven. Accumulated time off should be discouraged and should be allowed only in special circumstances. Annual vacation and sick leave with pay should be allowed.

Proper housing, adequate diet, and recreational facilities should be provided for all resident employees.

All personnel who are exposed to tuberculosis in the course of their work should have chest roentgenographic examinations every three months. For personnel who are not frequently exposed to tuberculosis within the hospital, chest roentgenographic examinations may be less frequent, depending upon individual circumstances, but in general an annual examination is probably adequate.

IX. PROTECTIVE MEASURES

For a number of years there has been a growing realization that it is advisable for exposed employees in tuberculosis hospitals to take precautionary measures against infection. As compared with persons in comparable age groups employed in other occupations, exposed employees in tuberculosis hospitals have a higher risk of developing the disease.[12] In order to effectively reduce the hazard, preventive measures are necessary.[13]

Sputum napkins: It has been shown that tubercle bacilli are given off when the patient coughs, sneezes, whistles, and talks. If these organisms can be "trapped" at their source, the degree of contamination of the patient's environment is greatly reduced. Holding paper napkins over the mouth and nose acts as a partial solution to the problem, but it takes a great deal of patience and perseverance to educate the patient along these lines because, prior to diagnosis of tuberculosis, most people are in the habit of coughing without covering the mouth and nose.

Napkins should be made of crepe paper of at least two thicknesses. They should be

[11] Riggins, H.: Is nursing in step with research? Tuberculosis control in hospital personnel, Nat. Tubere. A. Tr., 1952, p. 609.

[12] Mikol, E. X., Horton, R., Lincoln, N. S., and Stokes, A. M.: Incidence of pulmonary tuberculosis among employees of tuberculosis hospitals, Am. Rev. Tubere., 1952, *66*, 16.

[13] Safer Ways in Nursing to Protect Against Tuberculosis: A Guide for Precautions in the Care of Patients, National Tuberculosis Association, 1948.

6 by 6 inches or larger in size. A large paper bag should be available at the bedside for disposing of these napkins after they have been used. The bags should be picked up and burned every twenty-four hours or oftener.

Sputum cups: Usually when a patient coughs, sputum from the lungs is raised and should be expectorated, not swallowed. A paraffin-coated paper cup is best for the collection of sputum. Sawdust, or other absorbent material, placed in the bottom of the cup is often useful. These cups should never be allowed to become more than half full, and should be picked up and burned every twenty-four hours, or oftener. When the quantity of sputum is scant, sputum napkins may well be used instead of sputum cups.

Masks: It must be realized that there will be times when the patient will cough in his sleep; even during his waking hours he will at times cough or sneeze without holding his napkin over his mouth and nose. Employees should, therefore, be further protected by a mask. A mask properly constructed and properly worn so that it covers the employee's mouth and nose, forcing him to breathe through the mask, will afford him the maximum amount of protection.[14, 15] Masks should be worn when giving direct care to all infectious tuberculous patients and should be changed at least once an hour or when they become damp.

Gowns: Gowns should be worn in the contaminated areas to protect the clothing from contamination. These washable gowns need not be laundered after each wearing, but should be laundered after one day's wear, or oftener if they are grossly contaminated. Between each wearing, they should be hung so that the outside does not contaminate the inside of the gown.

Caps: The use of cotton caps is advisable when caring for infectious patients.

Hand-washing facilities: Frequent hand washing is necessary for workers in a tuberculosis hospital and, therefore, lavatories should be placed in convenient locations and in sufficient numbers to allow this procedure. These facilities should preferably be the foot-controlled or knee-controlled type, with a high gooseneck faucet.

Reduction of dust: The dissemination of infectious dust in the air can be reduced at bed-making time and sweeping time by the gentle handling of bed linen to prevent dust, lint, and organisms from being shaken into the air, and by the damp dusting and mopping of floors with cloths and mops which are laundered after use. The use of a vaccum cleaner, preferably with a water trap tank, is advantageous. The oiling of bedding with an emulsion of Triton® (T-13) and the use of a sweeping compound made of 2.5 gallons of paraffin oil to 100 pounds of sawdust have been helpful in the control of dust, but the use of a sweeping compound is not feasible for some types of floor covering.[16]

Laboratory: The search for tubercle bacilli has been intensified in recent years by culturing of sputum, gastric aspirates, and bronchial secretions. More recently, the testing of tubercle bacilli for their susceptibility to various chemotherapeutic agents has further increased the work and the chance of infection in the laboratory. In view of this, it is recommended that all sputum work be carried out in a separate room reserved for this purpose only, and that the workers wear cap, gown, and mask and do their culture work under a hood.

Morgue: Protective procedures should be used by both the examiners and observers

[14] McNett, E. H.: The face mask in tuberculosis, Am. J. Nursing, 1949, *49*, 32.

[15] Lurie, M., and Abramson, S.: The efficiency of gauze masks in the protection of rabbits against the inhalation of droplet nuclei of tubercle bacilli, Am. Rev. Tubere., 1949, *59*, 1.

[16] Loosli, C. G., Wise, H., Lemon, H. M., Puck, T. T., and Robertson, O. H.: The oil treatment of bedclothes for the control of dust-borne infection: II. The use of Triton® oil emulsion (T-13) as a routine laundry procedure, J. Hyg., 1946, *43*, 105.

when post-mortem examinations are made.[17, 18] Before the examination starts, all present should don cap, gown, and mask; the examiners should also wear gloves. The nostrils and mouth of the dead person should be plugged with cotton and, when the trachea is cut, the proximal end should also be plugged with cotton. If the lungs are to be studied bacteriologically, it is advisable to section them under a laboratory hood. If the lungs are to be studied from a pathologic standpoint, it may be desirable to distend them, after their removal from the thoracic cage, with Kaiserling's solution or formalin. They can be sectioned at a later date.

When the post-mortem examination has been completed, the body should be wrapped in semi-absorbent paper sheets and then in heavy wrapping paper. (This can be easily accomplished by placing the body on a narrow table over which has been spread heavy wrapping paper, eight feet long and five feet wide, and then the semi-absorbent paper sheets, bringing the sides of the paper up over the body. In this way a relatively clean exterior is afforded the undertaker.)

The liberal use of ultraviolet light both during and after the examination is recommended.[19]

BCG: While not a substitute for any of the above technical procedures, the vaccination of tuberculin-negative employees will give them further protection.

Examinations: Not only do employees need to be protected from patients, but patients need protection from the possibility of infection by employees. This protection can be partially afforded by a pre-employment examination consisting of history, physical examination, chest roentgenogram, tuberculin test, Widal and Wassermann tests, and smallpox vaccination. Subsequent examinations should be made at intervals of three to twelve months, depending on the intimacy of contact with the patient or patient's fomites.

Visitors: It is likewise advisable to protect patients from visitors and vice versa. It is, therefore, advisable that at least a mask be worn by visitors of infectious patients.

X. SPECIAL SERVICES

The social service needs of patients are of utmost importance because tuberculosis creates for them and their families so many social, emotional, and economic problems.[20, 21] These needs are greater than is generally appreciated. Directly with the patient and in liaison with community facilities, the medical social worker should help the patient and his family work out personal and family problems. Unless adequate provision is made for such service through accepted existing agencies, tuberculosis hospitals should employ a full-time social worker for each 200 patients or major fraction thereof.

Provision should also be made for the patient's religious needs.

Adequate provision should be made for recreation and for occupational therapy.[22, 23]

[17] Meade, G. M.: The prevention of primary tuberculous infections in medical students, Am. Rev. Tuberc., 1948, *58*, 675.

[18] Sloan, R.: The dissemination of tuberculosis from fresh autopsy material, New York State J. Med., 1942, *42*, 133.

[19] Lurie, M. B.: Experimental airborne tuberculosis and its control, Am. Rev. Tuberc., 1947, *55*, 124.

[20] Miller, P.: Medical social service in a tuberculosis sanatorium, Pub. Health Rep., 1951, *66*, August 3 and September 7.

[21] A Handbook on Social Services for the Tuberculous Patient, National Tuberculosis Association, 1951.

[22] Kiefer, N. C.: Occupational therapy in tuberculosis, Occup. Therapy, 1946, *25*, no. 6.

[23] Functions of the Occupational Therapist in the Rehabilitation of the Tuberculous, Proceedings of Conference on Rehabilitation of the Tuberculous, Washington, D. C., National Tuberculosis Association, 1946.

The occupational therapy program should be closely integrated with the rehabilitation program and should be aimed toward the patient's eventual vocational goal. The employment of one full-time registered occupational therapist for each 100 patients or major fraction thereof is recommended.

If children are accepted for treatment, adequate provision should be made for the continuation of their education. Instruction in high school subjects should be available to adolescents when the number of patients in this category is sufficient to warrant it. Adequate educational facilities for all patients within the institution are desirable. Such facilities should include a library with a service for bed patients. The instruction of each patient during hospitalization should be correlated with his physical condition, and his study time should be observed and recorded by the educational staff.

In institutions of 200-bed capacity or more, a formal education and rehabilitation program should be provided.[24, 25] This might be accomplished by coordinating with a senior clinician as head of the team the work of school teachers, occupational therapists, and medical social workers. The staff should include a resident counselor in vocational education and rehabilitation, with training at the professional level. In the absence of such a counselor as, for example, in the smaller institutions, the need could be met partially through cooperation with state vocational services. Efforts at rehabilitation should begin as soon as possible after the patient's admission. The rehabilitation program, geared to the patient's activity tolerance and eventual work capacity, should encompass vocational analyses, vocational training, including education and occupational therapy, in-hospital training to improve work tolerance, and job placement. Each patient discharged with medical consent whose rehabilitation has not been planned otherwise should be advised fully regarding the rehabilitation and placement services available in the community to which he is to return.

XI. SALARIES

Adequate compensation should be provided in order to attract and retain competent personnel. Salaries for employees should be in keeping with existing salaries and rates paid by other hospitals in the area, with additional recompense for the hazardous nature of the occupation.

The compensation for the director of the hospital and senior clinician should be governed by the size of the hospital, the location, whether or not maintenance is furnished, and should be somewhat in keeping with what these individuals might earn in the private practice of medicine based on their training and experience. Suggested annual salaries for full-time hospital directors are listed below.[26] With yearly increments for satisfactory service, the salaries can be increased from minimum to maximum.

Size of hospital	With Maintenance		Without Maintenance	
	Minimum	Maximum	Minimum	Maximum
100 beds or less	$8,000	$10,000	$12,000	$14,000
100 to 200 beds	10,000	12,000	14,000	16,000
200 to 400 beds	12,000	14,000	16,000	18,000
400 beds or over	14,000	16,000	18,000	20,000

[24] PATTISON, H. A.: Rehabilitation of the Tuberculous, The Livingston Press, 1949.
[25] The Rehabilitation Team, National Tuberculosis Association, 1951.
[26] Hospital Counselor, American College of Chest Physicians, Chicago, Illinois.

XII. TUBERCULOSIS DEPARTMENTS IN GENERAL HOSPITALS

Tuberculosis wards of general hospitals should, with minor exceptions, aim to meet the foregoing standards for tuberculosis hospitals. With strict communicable disease techniques, tuberculosis patients can be treated in such special tuberculosis units without serious hazard to personnel and other patients.

Correlated with this service should be a program of chest roentgenographic examination of all outpatients and all hospital admissions. Otherwise unknown tuberculosis cases treated in the hospital or the outpatient department may be a source of infection of personnel and other patients. Likewise, all employees should have chest roentgenographic examinations to exclude those with active tuberculosis.

XIII. TUBERCULOSIS DEPARTMENT IN MENTAL HOSPITALS

The standards for tuberculosis hospitals can, with minor exceptions, be applied to tuberculosis units in mental hospitals. Patients may be segregated in wards at each mental hospital, but centralization of the facilities for the treatment of tuberculosis in mental hospitals is preferable. Such centralization helps to provide better therapeutic facilities for the patients and also tends to limit the number of employees exposed to infectious cases of tuberculosis. Complete services for the modern medical and surgical treatment of tuberculosis by qualified medical personnel should be provided and should meet the foregoing standards for tuberculosis hospitals. Of particular importance is the provision of adequate bacteriological and clinical laboratory services, and thoracic surgery for all patients who need it.[27]

The tuberculosis control program should include chest roentgenographic examination of all patients and new admissions to mental hospitals, and all employees in these institutions. Periodic re-examination of these groups is also necessary.

Because of the patient's inability to cooperate in many instances, strict communicable disease technique and a constant educational program in prophylaxis and prevention of tuberculosis for nurses, attendants, and other exposed workers is most advisable.[28]

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HAROLD G. CURTIS
FRANK L. JENNINGS
HERMAN J. NIMITZ
EDWARD N. PACKARD
RALPH HORTON, *Chairman*

[27] AMERICAN TRUDEAU SOCIETY: Report of the Committee on Tuberculosis in Mental Hospitals, Am. Rev. Tuberc., 1946, *54*, 448.

[28] MARKLE, E. W.: A nursing care program for psychiatric tuberculous patients, Am. J. Nursing, 1950, *50*, 307.

NOTICES

ELECTION OF NEW OFFICERS FOR STATE TRUDEAU SOCIETIES

Nine state Trudeau Societies have reported the election of the following new officers:

Florida: president, Dr. Harold W. Johnston, Orlando; vice-president, Dr. Simon D. Doff, Jacksonville; secretary-treasurer, Dr. Howard DuBose, Lakeland.

Illinois: president, Dr. George C. Turner, Chicago; president-elect, Dr. Ernest Teller, Chicago; secretary-treasurer, Dr. George H. Vernon, Edwardsville.

Indiana: president, Dr. Donald W. Brodie, Indianapolis; president-elect, Dr. Stuart R. Combs, Terre Haute; vice-president, Dr. Arvine G. Popplewell, Indianapolis; secretary-treasurer, Dr. C. J. McIntyre, Indianapolis.

Iowa: president, Dr. Walter Kirkendall, Iowa City; president-elect, Dr. Eugene B. Floersch, Council Bluffs; vice-president, Dr. Daniel F. Crowley, Jr., Des Moines; secretary-treasurer, Dr. Paul M. Seebohm, Iowa City.

Kentucky: president, Dr. Adam Miller, Lexington; vice-president, Dr. Joseph K. Newton, Outwood; secretary-treasurer, Dr. E. R. Gernert, Louisville.

Louisiana: president, Dr. Walter McCook, Shreveport; president-elect, Dr. Thomas C. Black, Alexandria; secretary-treasurer, Dr. Lawrence H. Strug, New Orleans.

Nebraska: president, Dr. Donald R. Jackson, Omaha; vice-president, Dr. Max Fleishman, Omaha; secretary-treasurer, Dr. L. C. Albertson, Omaha.

Massachusetts: president, Dr. Edward J. Welch, Brookline; vice-president, Dr. Norman J. Wilson, Brookline; secretary-treasurer, Dr. Kenneth T. Bird, Boston

Wisconsin: president, Dr. Raymond H. Evers, Plymouth; vice-president, Dr. Helen Dickie, Madison; secretary-treasurer, Dr. John T. Mendenhall, Madison.

AMENDMENTS TO SOCIAL SECURITY ACT WITH RESPECT TO THOSE SUFFERING FROM LONG-TERM PHYSICAL OR MENTAL DISABILITIES

Physicians, hospitals, and clinics will have an important part in assisting their patients to get the benefit of a new provision of the social security law which protects a worker's social security record while he is disabled.

A person who is unable to work because of mental or physical disability, or who is blind, can have his social security earnings record "frozen" under the new law.

The effect of this action is similar to that of the waiver of premium in life insurance policies. It provides that the benefit payable to the person when he qualifies, or to his family in case of his death, will not be reduced because of the period in which he had no earnings.

Persons already receiving monthly old-age insurance benefits, if they were disabled for a considerable period of time before they reached 65, may have their benefits increased under the new law beginning with payments for July, 1955.

The new law protects the social security records of people

> who have been in work covered by social security for 5 of the 10 years before they were disabled, and for 1½ of the 3 years before they were disabled; who are unable to engage in substantial gainful activity because of a medically determinable impairment which is expected to be of long-continued or indefinite duration; and who apply to have their records frozen while they are disabled and after they have been disabled 6 months or more.

A determination that a person is disabled must be based upon medical evidence. The patient himself is expected to secure the initial medical evidence; therefore, he will fre-

quently request a summary of the history, clinical findings, and treatment of his case from his physician or medical facility. In other cases the request, along with a release signed by the patient, may come from the State agency responsible for the determination of disability, or from the Social Security Administration.

The medical reports will advance the patient's welfare if they are completed promptly and accurately, with sufficient detail to support the diagnosis.

The Social Security Administration hopes that many applicants can be returned to productive work through Vocational Rehabilitation services. Work in connection with rehabilitation services or in a "sheltered workshop" will not prevent a finding of current disability. Further information regarding the new freeze provision is available from your nearest social security office.

VI. NATIONAL CONFERENCE ON TUBERCULOSIS AND SILICOSIS

The Sociedad Mexicana de Estudios sobre Tuberculosis y Enfermedades del Aparato Respiratorio takes pleasure in inviting all resident and foreign physicians to the Sixth National Congress on Tuberculosis and Silicosis which will be held in the City of Mexico, January 23–29, 1956. For further information address: Balderas s 32 312. Ap. Postal s 7267, Mexico, D. F.

1956 Prize Essay Contest

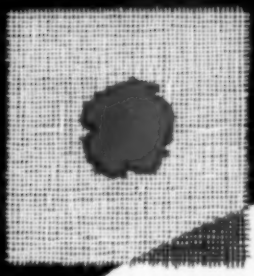
The Council on Undergraduate Medical Education of the American College of Chest Physicians offers three cash awards to be given annually for the best contributions prepared by undergraduate medical students on any phase in the diagnosis and treatment of chest diseases (heart and/or lungs).

The first prize will consist of a cash award of $250.00; second prize will be $100.00; and third prize, $50.00; each winner will also receive a certificate of merit.

The winning contributions will be selected by a committee of chest specialists and will be announced at the 22nd Annual Meeting of the American College of Chest Physicians to be held in Chicago, Illinois, June 7–10, 1956. All manuscripts become the property of the American College of Chest Physicians.

Applicants are requested to study the format of DISEASES OF THE CHEST, the official journal of the College, as to length, form, and arrangement of illustrations to guide them in the preparation of the manuscript. A copy of the College journal will be sent upon request. The following conditions must be observed:

1) The completion of an application form, which may be obtained by writing to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U.S.A.
2) Five copies of the manuscript typewritten in English (double spaced) should be submitted to the College offices in Chicago not later than April 10, 1956.
3) The only means of identification of the author shall be a motto or other device on the title page and a sealed envelope bearing the same motto on the outside, enclosing the name and address of the author.



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1. Owings, C. B.: The Control of Postoperative Bleeding with Adrenosem, Laryngoscope, 55:31 (January) 1955.
2. Peele, J. C.: Adrenosem in the Control of Hemorrhage from the Nose and Throat, A.M.A. Arch. of Otolaryng. 61:450 (April) 1955.
3. Riddle, A. C., Jr.: Adrenosem Salicylate: A Systemic Hemostat, Oral Surg., Oral Med., Oral Path. In press.

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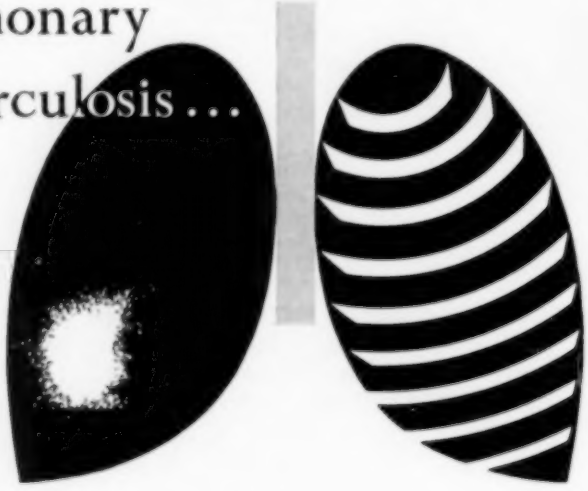

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1. Dobkin et al.: Anaesthesia, October, 1955.

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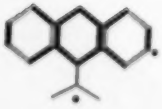

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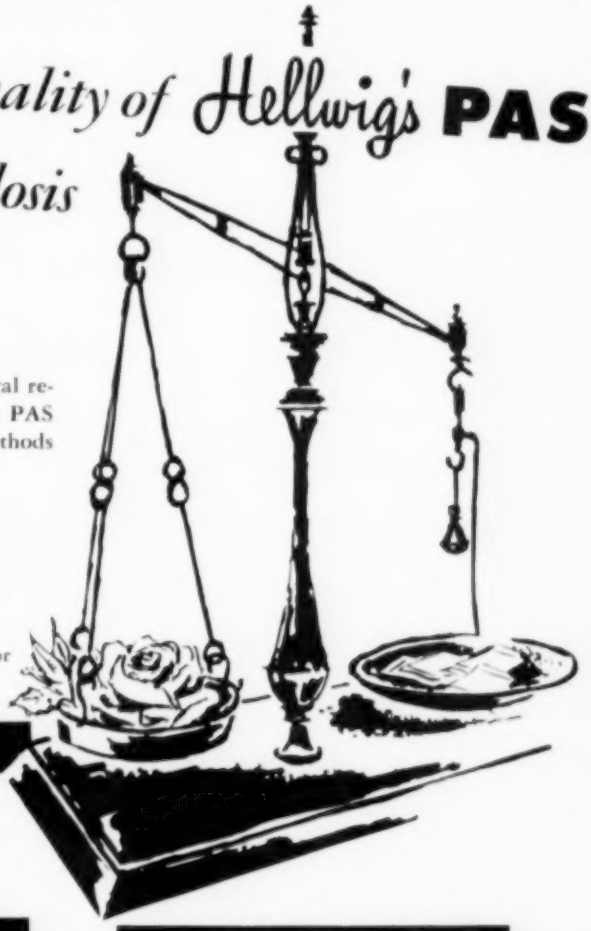

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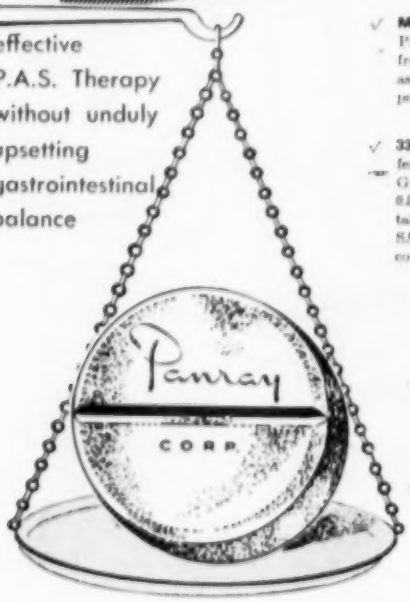

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